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OF THE

CONGRESS

OF

American Physicians and Surgeons

THIRTEENTH TRIENNIAL SESSION

HELD AT

WASHINGTON, D. C.

May 5th and 6th, 1925

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1.

This organization shall be known as the

CONGRESS OF AMERICAN PHYSICIANS AND SURGEONS.

2.

It shall be composed of national associations for the promotion of medical and allied sciences.

3.

It shall hold its sessions triennially in the city of Washington, D. C.

4.

The officers of the Congress shall be a PRESIDENT, VICE-PRESIDENTS, A SECRETARY, A TREASURER, AND AN EXECUTIVE COMMITTEE.

5.

The PRESIDENT shall be elected by the Executive Committee, of which he shall be *ex-officio* a member. He shall preside at the sessions of the Congress. He shall deliver an address.

6.

The PRESIDENTS of the participating societies shall be *ex-officio* the VICE-PRESIDENTS of the Congress.

7.

The SECRETARY and the TREASURER shall be elected by the Executive Committee. They shall be *ex-officio* members of the Executive Committee.

8.

The EXECUTIVE COMMITTEE shall be composed of one (1) member from each participating Society and said members shall be elected by the various Societies at the next annual meeting subsequent to the Congress.

It shall be charged with all duties pertaining to the organization of and preparation for the ensuing Congress, including the election of all officers and of a Committee of Arrangements.

It shall superintend the publication of the Transactions of the Congress.

9.

The expenses of the Congress shall be divided between the participating Societies in proportion to their membership.

10.

The admission of new associations to participate in the Congress shall be by unanimous vote of the EXECUTIVE COMMITTEE.

MINUTES

The thirteenth triennial session of the Congress of American Physicians and Surgeons was held in the Hall of Nations of the Washington Hotel, in Washington, D. C., on May 5th and 6th, 1925, according to the programme as ordered by the Executive Committee.

The first session was called to order at 8 P. M., Tuesday, May 5th, by the first Vice-President, Dr. Arthur L. Chute of Boston. Dr. William J. Mayo then delivered his address on "Contributions of Pure Science to Progressive Medicine."

On the following day the meeting was called to order at 2.30 P. M., by the President, Dr. William J. Mayo. The subject to be considered was "The Ductless Glands." Papers were read by Dr. John J. Abel of the Johns Hopkins Medical School, Baltimore, on "General Considerations in respect to the Harmones"; by Dr. Charles G. Stockard of the Cornell Medical School, New York City, on "The Gonads and Sex Physiology"; and by Dr. Walter B. Cannon of the Harvard Medical School, Boston, on "Some General Features of Endocrine Influence of Metabolism." These papers were discussed by Dr. Lewellys F. Barker of Baltimore, and by Dr. Harvey Cushing of Boston.

Adjournment.

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By Invitation of the Executive Committee.

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*Dr. John D. Kernan,	New York City.
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Dr. Howard A. Lothrop,	Boston, Mass.
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The following were present as

VISITORS.

to various of the component Associations.

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Dr. S. C. Harvey,	New Haven, Conn.
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Dr. Julian M. Howe,	Washington, D. C.
Dr. William F. Jacobs,	Buffalo, N. Y.
Dr. William A. Jewett,	Brooklyn, N. Y.
Dr. R. W. Johnson, Jr.,	Baltimore, Md.
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Dr. Rinyor Kauamara,	Niigata, Japan.
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Dr. Thomas Wheeldon,	Richmond, Va.
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Dr. Edwin B. Winnett,	Des Moines, Iowa.

RECAPITULATION.

	Emeritus, Senior, Active and Associates.	Corresponding.	Honorary.	Present.
American Ophthalmological Society ..	188	..	1	..
American Otological Society	125	..	5	..
American Neurological Society	195	..	23	96
American Gynecological Society	91	..	38	63
American Dermatological Society	88	15	9	60
American Laryngological Society	110	23	4	60
American Surgical Association	207	..	20	130
American Climatological and Clinical Association	170	8	15	89
Association of American Physicians ...	272	4	8	147
American Association of Genito-Urinary Surgeons	75	10	4	50
American Orthopedic Association	112	7	7	62
American Pediatric Society	89	..	9	60
American Association of Pathologists and Bacteriologists	389	..	..	..
American Society of Tropical Medicine	205	28	16	..
American Association of Immunologists	189	..	..	..
American Association for Thoracic Surgery	94	..	6	51
	2599	95	165	868
Total membership of Congress		2859		
Guests and Visitors				101
Total attendance				969

THE PRESIDENT'S ADDRESS.

WILLIAM J. MAYO, M.D.
Rochester, Minn.

CONTRIBUTIONS OF PURE SCIENCE TO PROGRESSIVE MEDICINE.*

Archaeologists in search of evidence of the development of the sciences have earnestly studied the meager historical records of Egypt's ten thousand years, and while relics of interest in the general arts and sciences have been found, comparatively little of value from the standpoint of medicine has been unearthed, perhaps because of the eight complete reversions to barbarism which buried the seats of Egyptian culture in the sands of time.

It was not until the fourth century before the Christian era that the ancient Greeks, largely through the contributions of two men, gave evidence of a love for medical science. We look back to Hippocrates as the founder of clinical medicine. He was one of the first to free himself from the shackles of superstition. Observing carefully the manifestations of disease, in the light of the knowledge extant, he critically traced, so far as he was able, various disease processes from origin to termination. To the genius of Hippocrates' near contemporary, the great Aristotle, we owe the development of the deductive method of reasoning, on which science has rested securely. Aristotle was interested in all living things, in the method of growth, life processes, and in the manner in which life terminated. The Aristotelian methods were to endure for two thousand years unchallenged by a competitor.

It was not until the seventeenth century, the Shakespearean period, that inductive methods of reasoning were emphasized by Bacon, and extended in the nineteenth century by the logic of Mill. In the seventeenth century these newer methods were applied to medicine by William Harvey, the founder of modern physiology. We think of Harvey in relation to the circulation of the blood, but we should think of him rather as the founder of experimentation and research, as the builder of methods by which controlled experimentation, often vivisection, could be made to parallel clinical experience.

Sydenham, of precious memory, was the clinician of Harvey's time, and what Hippocrates was to Aristotle, Sydenham was to Harvey. Sydenham, with a clear mind and a hatred for sham and hypocrisy in medicine, gave us the finest insight of all time into clinical medicine as related to current knowledge. While we look upon him as the founder of sound theories of the causation and classification of fevers, this investigation was merely one expression, and that almost incidental, of his clinical acumen, which led to many advances in medical science.

The seventeenth century produced another man about whom we have heard too little, John Mayow, who was one of the first of the physician chemists. The observations and experiments of Mayow led later to the discovery of oxygen, and to-day, after nearly three hundred years, we are just beginning to understand those fundamental problems which connect physicochemistry with the medical sciences. The impetus given by the work of Harvey, Sydenham, and Mayow led to rapid advance in knowledge of the sciences, in relation to clinical medicine.

Of those who carried on these researches, the outstanding names were John and William Hunter, who, in the latter part of the eighteenth century did so much to put medicine on a sound foundation. John Hunter had that divine discontent which leads to progress. He was the first to study pathology as a whole, and it was he who related general pathology to clinical medicine. Previous to Hunter's time, great truths were discovered in pathology and medicine, but they were largely isolated and uncorrelated. John Hunter, with the eye of the master, saw in these variations of vital processes the fundamental similarity due to common origin. When one goes to the Hunterian Museum at the Royal College of Surgeons of England and looks at those wonderful specimens, 14,000, prepared and labelled in black by Hunter's own hand, so beautifully preserved that even after more than one hundred years they compare favorably with the best we are able to prepare to-day, one can readily understand the profound influence that Hunter exerted on modern medicine, of which he sometimes has been called the father. Hunter was interested in animal experimentations. It is told of him that after attending a meeting at which Jenner had propounded his theory of vaccination for small-pox, Hunter the next morning wrote Jenner a letter saying, "Why submit hypotheses? Try it on hedgehog and know."

William Hunter, the physiologist, approached the normal functions of life with a remarkable understanding, and correlated them by the inductive method.

Advance in clinical medicine since the time of the Hunters has been rapid. Workers in pure science, engaged in fundamental research, have given the clue to the solution of many problems in clinical medicine. Recently there was celebrated the centenary of the birth of the chemist physician, Pasteur, whose epochal studies have been of greater service to mankind than those of any other known human being. Pasteur drew from the foundations of pure science inspiration which led to the discovery of new knowledge, on which was to develop the germ theory of disease. To the characteristic patience and thoroughness of the German school we owe the extraordinay development of the relation of Pasteur's discoveries to the microbic origin of disease, Virchow's studies in cellular pathology, and Schmeideberg's development of pharmacology, contributions of the greatest importance to the science of medicine.

Even a brief retrospect shows the lasting influence of Greek culture, the dominance in the middle and later historical periods of the English scientific school, the great contributions of the French, and last, the development of Teutonic methods. The torch has been handed to America to light the way. Europe is exhausted by strife, disrupted by racial hatreds, the ills of to-day cloud the horizon of the continental to-morrow.

The sciences bring into play the imagination, the building of images in which the reality of the past is blended with ideals for the future, and from the picture there springs the prescience of genius. The influence of the eye has been dominant in the development of science. Units in science are ultimately measured by visual methods. In the development of the special cranial senses in man, those of taste, smell, and hearing do not influence cerebral activity as directly as in other animals, but around the sense of sight were built most of the higher cerebral functions.

The great progress of science in the last generation has come largely through mechanical aids to vision, which have permitted the concentration on scientific problems of the full power of human intelligence. In the time of Harvey, microscopes were mere magnifying glasses, and those of the Hunterian school were not much better. The French, largely because of their development of better

types of microscopes in the nineteenth century, became prominent in scientific research. One may well say that the Zeiss Optical Works of Jena, aiding the eye in the investigation of the minute, and responding to the demand of science, contributed greatly to the progress of the Germans. The microscope, the x-ray, the exploratory incision, all have been subservient to the eye in the building of modern scientific medicine, the foundation stones quarried from the post-mortem, the edifice built from the "pathology of the living" as so aptly stated by Moynihan.

Sometimes, however, the microscope has failed, not because the object of study has been ultramicroscopic, but rather from lack of characteristics sufficiently distinctive for its detection. Many of the protozoa and bacteria have protective coloring which prevented their detection until the introduction of vital stains brought to the aid of the microscope distinctive coloring, and permitted the recognition with marvelous accuracy of microörganisms, such as the bacillus of tuberculosis and the spirochete. The cultivation of bacteria in suitable mediums has made easy their precise study. Cultural adaptability and selective localization of the bacteria of the streptococcus group have played an important part in the work of Rosenow, who has clarified the study of focal and concealed infections.

The whole fabric of the great advances in biologic science in the last generation was woven with microscopy, but the microscopic limit of 1/10 micron or 1/250,000 inch has been reached. The eye, aided by the microscope, was able to reveal not only the objects themselves, but usually also their size, shape, color, and other distinctive characteristics. All the particulate substances studied were obedient to well understood laws, for instance, gravity. To-day we face the ultramicroscopic field in relation to scientific progress as our forebears faced the realm of science when Pasteur promulgated his theories. Again, it is the eye that carries us forward.

When Brown, the English botanist, working in Bristol, began the observations which culminated in his written communication of 1827, he focused attention on a subject of enormous importance. The questions he raised a century ago require all the resources of modern science for an answer. Brown noted, as man undoubtedly had noted from time immemorial, that when a pencil of bright light was thrown into a dark room, there were to be seen in the air certain rapidly

moving particles of which there was no other physical evidence. On experimentation he noted with the microscope the continual movement among minute particles suspended in a liquid. Because of his investigations, the peculiar vibratory motions of these particles were called Brownian movements. The most important contribution to a proper understanding of these phenomena was that of Thomas Graham, Master of the Mint in London, who in 1861 published his painstaking observations which led to the first detailed description of colloid bodies. Graham's work was largely based on dialyses of colloid-sized substances through parchment paper. These observations led to the investigation of the colloid field, which included those ultramicroscopic particles lying between 1/10 micron and 1/1,000 micron, or 1/250,000 inch and 1/25,000,000 inch.

It was demonstrated ultimately that colloids formed suspensions, not true solutions, that colloids were of sufficient size to reflect rays of light, so that the particles might be studied. With the ultramicroscope, shadows of minute particles 1/100 micron or 1/2,500,000 inch in diameter can be seen. The great percentage of colloid particles, however, are infinitesimal, beyond discovery by the ultramicroscope, detectible only by the diffraction of light in suspensions, or coloring in the mass, as by dyes. A ray of light will pass through a true solution without diffraction, while it will be diffracted by even the finest of colloid suspensions. The disclosures of the colloid field have supplied the knowledge lacking with regard to substances that lie between those things which can be seen with the eye aided by the microscope, and the molecule and the atom, physical knowledge of which depends on other scientific evidence. Tyndall also called attention to these curious phenomena occurring in the track of a luminous beam (called the Tyndall phenomenon), the colorings of which are the result of sunlight striking colloids in the air. The rainbow is due to refraction of light by colloids. The colloid field is now being actively investigated and has yielded extraordinary results in agriculture and the industries.

Water may exist in a molecular form, and as a vapor it does not respond so readily to the attraction of gravity. Under specific atmospheric conditions, however, as when the evaporated water rises to a height where the air is rarefied, and where greater coldness exists than at the point of evaporation, it gathers together in colloid form as clouds. For rainfall of an inch to an acre, 100 tons of

colloid water, practically unresponsive to the force of gravity, is suspended over each acre; when the change from a dispersed to a condensed state has taken place, gravity causes the water to fall as rain, while the electrical energy on the surface of the colloidal particles may be given off as lightning and thunder.

The agricultural physicochemist, Gortner, and his pupils may influence the feeding of the world by their discoveries of the importance to plants of water in a bound form. The difficulties which stood in the way of finding food plants which would withstand winter killing were enormous. Years of patient waiting were often necessary before weather conditions suitable for the demonstrations could be encountered. When Gortner investigated the possibility that water might exist in a found state uninfluenced by ordinary atmospheric or thermic conditions, he found that if plants which did not winter kill were compressed in a hydraulic press, little or no juice, or free water, was obtained, and that the amount of juice that could be expressed was directly proportional to the ability of the plant to withstand frost. Carrying out his experiments in the desert, in conditions of drought, he found that plants which could withstand dryness contained water, but in a bound form. Experiments in the properties of water under compression, one of the most incompressible of all substances, have shown that the water in a film on colloid surfaces occupies only 75 per cent of its former volume, and that under such conditions it behaves as a solid and does not evaporate at 300° C. in a complete vacuum.

From colloid chemistry there is now being built a new physiology of man, a better understanding of vital phenomena and their relation to the metabolic processes, internal secretions, and immunizing substances.

The most extraordinary knowledge has come from the pure science of physicochemistry. Sir William Bayliss has well said that the dividing line between physics and chemistry has disappeared, that only under certain physical conditions, colloidal or molecular, can there take place the electric exchange of electrons and protons in the atomic field. A remarkable fact is that colloids, atoms, molecules, and electrons, unlike particulate substances which are microscopically visible, remain in rapid motion more or less permanently suspended in their medium in spite of the force of gravity, although all are affected by pressure, temperature, and atmospheric conditions.

In the years from 1803 to 1807 Dalton promulgated the atomic theory and investigated the constitution of the molecule, with so few instruments of precision that the exactness of his results bordered on the miraculous.

Moseley, the brilliant young English physicist, who lost his life in the Gallipoli campaign at the early age of twenty-eight, was able to show by an analysis of the atom through x-ray diffraction that there were ninety-two possible elements between hydrogen, the lightest, and uranium, the heaviest, all but four of which are now known, and that between each two elements in the progression of atomic weight there was approximately the weight of one or more atoms of hydrogen. The atom of hydrogen is made up of one electron in rapid motion around the single proton which forms the nucleus. An atom of carbon has twelve protons and twelve electrons, an atom of oxygen sixteen protons and sixteen electrons, an atom of gold 196 of each, and an atom of mercury 200 of each. The accuracy of these conclusions has been somewhat spectacularly confirmed by Miethe, who was able to convert the atom of mercury into one of gold. Economically the experiment was a failure, since it would have cost $30,000 to produce one dollar's worth of gold, but scientifically it was epochal, since it showed that the alchemist's dreams of the transmutability of metals were not idle. The electromagnetic vibration of the x-ray is approximately from 1/100,000,000 to 1/1,000,000,000 inch in length smaller than the atom itself, a fact which has made possible the refractive process by which these measurements were made.

Bohr, the Danish investigator, following Rutherford's nuclear theory, pictures the atomic system as a solar system in which the sun is represented by a nucleus of positive electricity and the planets by rapidly revolving negative electrons; and on this theory he has calculated the wave length of light in each line of the hydrogen spectrum. Rutherford, Thomson, Ashton, and many other research workers have demonstrated that about the nuclei are electrons free or loosely attached, which has been given the name of valence electrons, and it is the study of the exchange of these arrangements that we speak of as chemistry.

As shown by Arrhenius, the Swedish investigator, true solutions of electrolytes in water under certain conditions are ionic, and it is the separation into positive and negative ions that makes chemical

exchanges possible. Since life depends on chemical changes, it is not surprising that 75 per cent of the human body should be composed of water and complex aqueous systems.

Oxygen contributes on the average 47 per cent of the atmosphere, water, and the known earth. Considering that the base of the brain can live only from seven to ten minutes without oxygen, it is surprising that there is in the body no mechanism for storing a reserve of oxygen or producing it under stress. All life is the result of combustion. Oxidation, or the union of various elements with oxygen, gives rise to the heat and energy necessary for life processes. This can also be expressed in terms of electrical charges. All foods contain carbon, hydrogen, and oxygen. The carbohydrates include the sugars, the coal of the body, which commonly furnishes heat and energy. The excess fuel is stored as fat, which again is composed of carbon, hydrogen, and oxygen in different combinations.

A study of the fats explains the ability of the camel to go with little water or food for long periods, and how life is maintained in hibernating animals. While the sugars undergo rapid metamorphosis, the hydrogen in the fats is not so rapidly dissociated from carbon, and the result of its oxidation is the slow production of heat, energy, and notably, water, all of which are so necessary to life. The amino acids resulting from protein metabolism are readily convertible into sugar. All proteins contain nitrogen, and most of them a little sulphur, elements which give form and stability to the tissues and facilitate the deposition of other elements, such as calcium.

It is in the tissue colloids that molecular dissociation of hydrogen permits the combination of carbon and oxygen which gives rise to energy and heat. The resultant carbon dioxid passes into the venous capillaries and to the lung for elimination. When certain toxic poisons, for instance, histamin, paralyze the contractile cells in the capillary wall, the colloids of the blood plasma pass from the capillaries into the tissues, and produce the condition known as shock.

Perkin, working in the Royal College of England in 1856, discovered the dyes in which he was unable to interest England. His student, Hofmann, took this new knowledge back with him to Germany, under whose control it gave rise to many useful drugs as well as explosive.

Colorimetry has been of extraordinary value in aiding the eye to recognize the minute. Certain manifestations of electromagnetic vibration are recognized by the retina as colors. The longest ray

appears to the retina as red, and in order of the length of the rays, orange, yellow, green, blue, and violet are seen. On the relative length of these rays the colorimetric system is based. The production of colors en masse has facilitated the application of the dyes to the scientific study of the ultramicroscopic field. Evans has shown that the elimination of dyes from the blood-stream, when introduced intravenously, is purely a filtration phenomenon.

The results of the application of the pure sciences of physico-chemistry to clinical medicine has opened up a wonderful field. To-day restoration of the sick can be as precisely accomplished in the living body as similar chemical exchanges can be brought about in the test tube. The estimation of retained excretory substances is now accurately made from studies of the blood, whereas formerly they were inaccurately estimated from the excretions, as, for instance, the urine. The whole problem of excretory or filtration organs, such as the kidney, has been greatly simplified.

The kidney is to be looked on as a filter of molecular substances. Urea is one of the smallest of the molecules, and does not hydrate; that is, it does not absorb water and, therefore, does not change in size. The dye, phenolsulphonephthalein, used by Rowntree and Geraghty, apparently of the same filterability as urea, has made possible a ready test of urea filtration through the kidney. Rowntree also used the dye, phenoltetrachlorphthalein, which he found was excreted entirely through the bile as a test of the functional capacity of the liver. Rosenthal's splendid contribution, whereby the extent of retention of dye in the blood is determined in hepatic disease, has proved of very great practical value in clinical medicine. This test furnishes a fairly accurate conception of hepatic function.

Mann, in classic experiments, showed that after removal of the liver from the dog, no urea was formed in the body, and that sugar disappeared from the blood, but also that life in the dehapatized animal could be greatly prolonged by the intravenous introduction of glucose-salt solutions. The extraordinary remedial effect of this and similar measures, on toxemias of various kinds, gives a prevision of the future of medicine. We think of certain pathologic conditions as causing death, but death is brought about by altered function, and a true toxemia, for example uremia, affects the body as a whole. In those little understood toxic conditions associated with so-called high intestinal obstruction, mechanical obstruction is not necessarily present. These syndromes have been given various names, such as

acute dilatation of the stomach, and gastromesenteric ileus, and are similar to the toxemias seen at times following surgical operations and in the course of continued fevers.

When acute, these toxemias of high intestinal obstruction are accompanied by so profound a depression of vitality as sometimes to merit being called shock. The patients become dehydrated from excessive vomiting, the result of reverse intestinal peristalsis, and are either unable to take nourishment or unable to metabolize what they do take. The blood pressure goes down, subnormal temperature is associated with clammy perspiration, and sudden death often follows. The source of the disturbance lies in altered secretion of the duodenum and the high jejunum. In these cases the urea, which normally does not exceed 26 mg. for each 100 c.c. of blood, will usually be above 100, as much as 200 to 300 mg. or more. The urea represents the nitrogenous waste produce of protein metabolism. Creatinin, with a normal of 2 mg. in each 100 c.c. of blood, represents endogenous metabolism or tissue catabolism. When the creatinin blood content rises above 10 mg. it indicates a serious condition. The chlorids, with a normal of from 560 to 650 mg. for each 100 c.c. of blood, are greatly reduced; the reduction is frequently accompanied by alkalosis and signifies a profound change in metabolism. The carbon dioxid combining power of the blood plasma goes up from its normal, between 56 and 65 volumes per cent, and when above 100, tetany often ensues, which is another expression of alkalosis. Dehydration is a most marked characteristic, and indicates a concentration of the blood, leading to a failure of elimination and a profound alteration in the chemical constitution of the body.

Normally, complex carbohydrates are not available as such, but are decomposed into simple sugars before they are metabolized. Glucose is the specific form into which carbohydrates are converted before they can be utilized by the body. By intravenous introduction of glucose, chlorid of sodium, and the great solvent, water, we are able temporarily to sustain life. The introduction of a liter of 1 per cent chlorid solution with 10 per cent glucose two or three times in twenty-four hours, will often restore vitality in these patients and enable a life-saving operation to be safely undertaken. In other words, the great majority of these patients seriously ill can be rehabilitated before operation or aided in weathering the storms of readjustment following operation.

Physicochemistry of the human body concerns life itself. A

proper understanding of these vital processes is necessary to every man who practices medicine, no matter what his specialty may be, and as for the surgeon, the newer knowledge is changing his outlook. By calling to his aid the scientists, the internist, and the various specialists, he is able to bring relief to a large number of patients who formerly were looked on as beyond help, or, who unprepared for operation, were subjected to a high risk. Rehabilitation is to be a master word in medicine.

THE DUCTLESS GLANDS.

GENERAL CONSIDERATIONS IN RESPECT TO THE HORMONES.

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(Report Based on Stenographer's Notes.)

The lecturer made introductory statements in respect to discoveries in the field of endocrinology that were made by great leaders in clinical medicine of the past. With few exceptions, the dominant discoveries in this field have been made by clinical authors. It is they who have grouped the various syndromes and their relationships into clinical entities. The consequences of the ablation of the sex glands were appreciated very early in the history of mankind and it is only in modern times that the sex glands have been studied from the biological and clinical points of view. While not attempting to develop any thing like a history of endocrinology, the lecturer pointed out that contributions to this broad subject have been made in the past half century by representatives of every department of medicine as well as of biology and biochemistry.

The Theory of Chemical Principles Versus a Neurogenic Explanation of Endocrine Diseases.

It was pointed out that early investigators were generally inclined to a neurogenic hypothesis as explaining endocrine diseases. An attempt has even been made to bring Addison's disease under this category. The older men here will all recall the time when cases of Graves' disease were always referred to the neurological department and treated there. Moebius was the first to suggest in 1887 that Graves' or Basedow's disease is due to an abnormally increased activity—a hyperfunction of the thyroid gland in consequence of which an increased amount of the peculiar hormone of this gland, thyroxin, is thrown into the general circulation. Another well known example of conflict between these two hypotheses relates to the pancreas. In 1889 Von Mering and Minkowski performed their famous experiment showing that extirpation of the pancreas in the dog leads to diabetes mellitus in the animal and put forward their assumption that a definite chemical principle or hormone elaborated

by the pancreas best explained the occurrence of the diabetes. The distinguished physiologist, Pflüger, however, thought that this assumption was quite groundless and expressed it as his belief that the diabetes experimentally produced by Von Mering and Minkowski was due to section or injury of the autonomic fibers in the neighborhood of the duodenum and pancreas. In the last 30 years, however, the chemical or hormone theory of the endocrine disturbances has won out more and more. I would, however, have no one here believe, especially the neurologists here present, that it is my purpose to put the autonomic nervous system to one side in the discussion of endocrinological problems. This important division of the nervous system stands in very close relationship to many of the endocrine organs and the interrelationship between the two is a matter of active investigation in a number of laboratories throughout the world at the present time. Some writers enumerate about fifteen organs or structures of the body that may possibly elaborate hormones. I would say, however, that at the moment we are very far from demonstrating definitely that fifteen separate hormones are produced in the body. Certainly thyroxin, insulin, secretin, pituitrin, epinephrin and the hormones of the sex gland and of the parathyroids, must be accepted as proven examples of chemical messengers. It may be accepted that more principles of this kind will be definitely isolated from hormone-producing organs. To give only one example of a hormone still to be isolated I would refer to the one elaborated by the cortex of the interrenal organ. We are now living in the day of chemical messengers and allied principles of very great potency. The vitamines which we take in with our food are really hormones of extraneous origin and the list of substances that act in very dilute solution in the animal body is constantly being extended. Carrel, for example, has applied the term "trephones" to the substance or substances present in embryonic tissue juice which is necessary for the proper growth of fibroblasts from a fragment of the embryonic heart of a chick during so-called tissue cultures. These trephones or growth-promoting substances were found also in leukocytic extracts as well as in embryonic tissue and I think they may very properly be classed as a group of growth stimulating hormones. You will recall that we have an extraordinary substance of allied character capable of influencing the growth of bone and other tissues which is present in the anterior lobe of the hypophysis and which has not yet been isolated as a chemical individual. Many botanists

also find it necessary to assume the presence of definite chemical substances that influence the growth and repair of plant tissue, while a few botanists assume a skeptical attitude on this point. In fact I find it very interesting to study the botanical literature covering this controversy; the fact is that botanists began to speak of hormones at a time when the conception was quite new to animal physiologists and medical men. Many botanists even incline to the view that it is necessary to postulate the presence of correlated chemical substances or hormones in unicellular plants, or even for the individual cells of multicellular plants, in order to explain the interaction of the nucleus with other parts of the plant cell. The workers in the field of hormones will do well to study the extensive botanical literature bearing on the subject.

Hormones as Influencing and Modifying Structure.

Although only a small number of true hormones have been isolated and determined as chemical principles, it is nevertheless clear that biochemists and physiologists already have by the results of their study of these principles, thrown a bridge across the chasm that has hitherto separated biochemistry from morphology. I have only to remind you of the morphogenetic substance or substances that are produced in the anterior lobe of the hypophysis, substances which can affect the growth of bone and other structures to an extraordinary degree. One has only to recall the rôle this hormone plays in acromegaly and gigantism to admit the truth of the statement I have just made. Indeed both the distinguished anatomists, Sir Arthur Keith and Professor Bolk of Amsterdam, have expressed the conviction that the differentiation of mankind into racial types is based on the varying interaction of the internal secretory organs, And other far reaching consequences are hinted at by certain students of the hormones; personality, character and immunity, say these investigators, are all bound up with this question of the internal secretions. There are immense possibilities here open to future workers!

Interrelation of the Endocrine Organs.

Medical literature contains many articles dealing with pluriglandular syndromes. Dr. Hans Lisser, a conservative investigator in this field, writes "As a matter of fact, the majority of endocrino-

pathies which are justified in diagnosing, exhibit a predominantly uniglandular basis, which anyone properly trained in endocrine diagnosis should be able to recognize. A firm foundation for incretory therapy demands a sharply defined analysis of the symptoms and signs, with emphasis on the gland primarily responsible." And Timme believes, "the whole aspect of multiglandular syndrome is more or less confusing at the present stage of our knowledge." I shall not further discuss the clinical aspect of the problem, believing that conservative and keen critics among you will hold in check those in your ranks who would carry this matter beyond what is justifiable in the present state of our knowledge. There are numerous experimental facts, and more are being brought to light almost daily, that prove that certain definite interrelations exist between the endocrine organs. One has only to recall the studies that have been published by morphologists, anatomists and experimental zoologists in reference to the results of ablation of the sex glands to be convinced of this point. Professor Stockard will, I hope, give you the results of some of his studies in this field. Certain definite alterations produced in other endocrine organs by the removal of the sex glands are now being studied by experimental biologists as never before. Seitz has recently published the results of experiments made with the intention of learning what influence, if any, is exerted on the young *in utero* by certain of the glands of internal secretion of the mother. He removed from male and female rabbits the whole or part of the thyroid and of the adrenal glands and then carefully examined the progeny. The young of the rabbits with ablated thyroids were found to have a distinct hypertrophy of the pituitary gland, quite as in the very different experiments cited above. There were noted not only an increase in the weight of the gland, as compared with normally produced young rabbits, but also microscopical changes of a definite character. In the young rabbits deprived of their suprarenal glands there was found an enlargement of the thymus and hypertrophy of the follicles of the spleen. It will be noticed that Seitz has found that it is more especially the allied glands of internal secretion of the young, rather than the homologous organ itself, that have undergone alterations consequent to removal of a certain gland of the parents. The effects were not always seen, but Seitz concludes that they were sufficiently frequent and sufficiently definite in character to leave no doubt as to their significance. Should these observations be confirmed, the important fact would be established

that the deficiency of a given hormone in the maternal organism is met by striking alterations in certain hormone-producing organs of the foetus. In this connection I would call your attention to Professor Evans' Harvey Lecture for 1924 entitled, "The Function of the Anterior Hypophysis." One of the main conclusions of this admirable address is given by Evans in the following words, "the hypophysis stands in a necessary relationship to normal function of the thyroid, sex glands and adrenal cortical tissue. Any explanation of how these effects are mediated constitutes part of the ill understood field of chemical dependencies and correlation within the body, ignorance of which cannot properly place in doubt evidence that correlation exists." These are but a few of the many experiments that may be cited in proof of our statement that an alteration in one of the endocrine organs may cause anatomical changes to appear in a distant but functionally interrelated endocrine organ.

Interactions of the Chemical Principles of Hormones Elaborated by the Endocrine Organs.

Although it is well established, as we have seen, that physiological and morphological interrelationships exist between endocrine organs, it has only recently been shown that the hormones themselves influence each other's action in the animal body. The relation between the two hormones, epinephrin and insulin, has recently been studied by Cannon and his collaborators by means of new methods. These investigators make use of the denervated heart of the cat, that is to say, a heart that has had its connections with all the parasympathetic and sympathetic fibers severed, as an indicator for an increased output of epinephrin, since such a denervated heart is subject only to influences via the blood stream. In cats thus prepared, insulin increases the rate of the heart beat. As the sugar percentage continues to fall, the heart rate continues to rise, the increased rate going as high as 36 beats per minute. The injection of glucose intravenously, when the heart rate is augmented and other evidences of sympathetic activity are present, is promptly followed by the disappearance of all these signs. After removal of one suprarenal gland and denervation of the other, or after removal of both glands the injection of insulin caused no acceleration of the heart, although the usual hypoglycemia occurred. This increased heart rate is explained as being due to a direct action of insulin on the adrenal medulla, in

consequence of which an increased amount of epinephrin is poured into the blood stream. Confirmatory evidence of such a "sympathomimetic" action of insulin is seen by Cannon in the facts that mydriasis and erection of hairs on the tail occurs in cats treated with insulin, and Yukujiro Abe, who has worked out this adrenalin-insulin action in Trendelenburg's laboratory, also concludes that the increased output of epinephrin is only one of the symptoms of a general stimulation of the sympathetic system, and points out, as Cannon has done, that in human beings mydriasis, increased perspiration and pallor of the skin are among the symptoms noted after large doses of insulin.

It should be stated that G. N. Stewart makes the criticism, "that it is very risky to assume that changes in the rate of the denervated heart occurring under such complex conditions, in the midst of such metabolic disturbances, are necessarily due to alterations in the rate of epinephrin output."

I hope that Professor Cannon, who is to follow me, will give you more examples of this sort of interrelationship as this is a field in which he and his pupils have made many very significant contributions.

Another example of this interaction concerns the hormone of the posterior lobe of the hypophysis and the pancreatic hormone, insulin. Cushing and his collaborators, Crowe and Hohmans, had shown some years ago that after removal of the hypophysis in dogs, these animals showed a high carbohydrate tolerance and that an injection of posterior lobe extract into a normal animal induced a hyperglycemia. Burns has recently shown that injection of insulin counteracts this hyperglycemic action of the posterior lobe principle. He finds, as Cushing did, that when the posterior lobe extract is injected by itself the blood sugar content goes up, when insulin is injected by itself into a properly prepared animal, the blood sugar falls, but when the two extracts are injected at the same time the blood sugar content remains at the normal level. Let me add but one more example of this interaction of the hormones upon each other. It has been shown by a number of investigators that when a thyroid extract is injected or when the thyroid gland in the living animal is induced by electrical stimulation to put an excess of its peculiar hormone into the blood stream, a subsequent injection of epinephrin will induce a very much greater and more prolonged rise of blood pressure than is seen under normal conditions. I cannot stop to give

other instances to prove that the hormones of the endocrine organs influence each other's action either in the way of augmentation or inhibition when administered in a manner appropriate to the experiment in hand.

The Mode of Action of a Given Hormone on a Given Tissue or Organ Depends upon the Chemical or Functional State of the Latter.

In almost all cases of hormone action we have to consider not merely the hormone itself but also the receptivity or functional state of the organ or organs which are to be affected. To give an example from clinical medicine in reference to this point: Keith suggests that the reason the hands and feet in acromegaly respond so easily and disproportionately to the growth hormone of the anterior lobe of the hypophysis lies in the fact that these organs are in more constant use and therefore respond more vigorously to this sensitizing growth hormone. This is only an exaggerated manifestation of the normal process, says Keith, and is due to flooding of the body with this hormone, for nothing is more certain than that hard manual labor will normally itself produce marked growth responses in the hands and feet, but this normal functional response never approximates to that seen in acromegaly.

Innumerable examples from the studies of modern pharmacologists and physiologists might be cited in support of our statement that the action of a given hormone is conditioned by the functional, or if you like, the chemical state of the organ or tissue upon which it acts. An oft cited example was discovered by Dale some years ago. He found that, after the intravenous injection into a cat or dog of a medium dose of ergotoxin and after waiting for the induced vascular responses to subside, an entirely abnormal response now follows an injection of an ordinary dose of the adrenal medullary principle. In place of the usually observed vasoconstriction and the resulting rise in arterial pressure, the exactly contrary physiological response is observed, namely, a prompt and decided fall of arterial pressure and a lessening of the heart rate. Later investigations showed that this reversal in the action of the adrenal hormone following a harmless dose of ergotoxin is not confined to the cardio-vascular response to the hormone but is equally true of its other effects. The liver, for example, will now no longer pour out an increased amount of sugar

into the blood as before the administration of ergotoxin. The work of recent years has shown that similar alterations in the activity of hormones are induced in general by any one of a number of organic or inorganic substances. The presence of one of these modifying agents in a given tissue may so alter its response to a given hormone that one may note either an increase or a decrease in its action, or, as in the case just cited, the exact opposite of its usual action.

The elusive circumstances that underlie these abnormal responses are often overlooked or misinterpreted, and consequently two or more separate physiological principles are sometimes postulated in place of one, as it seems more rational to do this than to credit a single hormone with a multiplicity of powers, not to mention the paradoxical property of having both positive and negative qualities. Thus, Schafer and his collaborators early demonstrated that an aqueous extract of the posterior lobe of the hypophysis cerebri induces a diuresis upon intravenous injection. Later, other investigators, more particularly clinical authorities, discovered that such extracts also have a marked antidiuretic action, a physiological property of which frequent use is now made in medical practice in moderating the excessive urination of diabetes insipidus. It was natural at this time for investigators to attribute these opposite actions to two distinct principles, one a diuretic, the other an antidiuretic substance. After I had succeeded in isolating the hormone of the posterior lobe of the hypophysis in the form of a highly active (if still somewhat impure) tartrate, this view could no longer be maintained. Dr. Geiling and I were able to produce either diuresis or suppression of urine at will in our experiments on rabbits. A diuresis which could be induced repeatedly and as often as desired was readily obtainable with rabbits that had been previously fed for five days, only with succulent vegetables, cabbage, spinach, etc., while animals fed without special attention to the nature of the food reacted to injections of the pituitary tartrate only with suppression of urine. The latter action is what might be called the normal action of the hormone, while its opposite or inverted action of secondary importance and of short duration only, is observed only when the chemical composition of the blood and tissues has undergone qualitative and quantitative alterations in consequence of a week's diet on watery vegetables. It is thus evident that one and the same hormone may act under given conditions in one way upon one animal and in precisely opposite manner upon a second animal of the same species.

Other analogous conditions under which this essentially antidiuretic hormone may induce a temporary diuresis are found in the administration of highly diuretic agents, such as sodium chloride, urea and glucose, as also in the employment of certain anesthetics. In reference to the manner of action of this hormone under these and other conditions, the recent work of Fromherz, Molitor and Pick, Smith and McCloskey, Stehle and Bourne, Craig, Starling and Verney and others should be consulted.

It has been shown repeatedly in recent years, as already stated, that the several hormones also mutually influence each other's action much in the manner just described. It may be stated in general terms, then, that a preceding or concomitant event, if I may use the term, conditions the action of a given hormone.

The Present State of Our Knowledge as to the Chemical Constitution of the Hormones.

Let us now take stock of where we stand as to our actual chemical knowledge of the hormones. Our chemical knowledge of the numerous hormones circulating in the body has reached a satisfactory status in respect to only two of their number, that elaborated by the thyroid and that by the medulla of the suprarenal gland. You are all more or less familiar with the fundamental chemical discoveries of Kendall of the Mayo Clinic in regard to the iodine-containing hormone of the thyroid gland, and it may truly be said, that next to the medullary principle of the suprarenal gland, the thyroid hormone is best understood from the chemical as well as the physiological point of view. Until, however, its synthesis has really been effected, the investigator must remain somewhat doubtful as to its ultimate chemical structure. The work of Kendall has been supplemented by the brilliant work of other experimenters at the Mayo Clinic, so that we are now in possession of a very great amount of knowledge in regard to the physiological and clinical value of this extraordinary hormone. The other hormone that has been worked up completely from a chemical point of view is epinephrin (adrenalin, suprarenin, adrenin, etc.). This special principle is found only in the medulla of the suprarenal gland and in other chromophil cells of the body. The mystery of its molecular structure has been solved by chemists. It has been prepared synthetically and it was quite in order for chemists to name it 1,2-dihydroxy-4^2-methylamino-

ethyl-4'-olbenzene, $C_6H_3(OH)_2(CHOH.CH_2NHCH_3)$—a designation which is shorthand for much sound chemical science.

It must be the aim of biochemists to elucidate the true chemical nature of insulin, of the post pituitary principle of the anterior lobe of the hypophysis, of the parathyroid principle, of the ovarian and testicular hormones—to mention only a few of the more important ones. Extraordinary difficulties are encountered in biochemical studies of this nature and we only make headway after we happen to elaborate new chemical methods, but progress is being made, although slowly. At the moment we are very much hampered by lack of definite information as to the true chemical composition of the great majority of the hormones. I believe it is only a matter of time, even though the goal must be set far in the future, when these unstable substances will yield to the investigator the secrets of their composition and the rationale of their operations within the body.

THE GONADS AND SEX PHYSIOLOGY.[1]

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The gonads or sex glands are extremely complex even as compared with other glands of internal secretion. This complexity is largely on account of the fact that the gonad is not only a gland of internal secretion but is also the reproductive organ of the individual and is, therefore, intimately involved in the entire sex problem. It is a point of some biological interest that the gonads are the only endocrine organs in the vertebrate which may be directly compared with a similar organ in the body of the invertebrate. All other vertebrate glands of internal secretion are either absent from the invertebrate body or have been nomologized with most dissimilar structures. Strangely enough, however, the gonads of the invertebrate seem comparable only to those of the vertebrate in being organs of reproduction or germ glands, there being no recognized internal secretion. The comparable parts of the gonads in the vertebrate and invertebrate are simply, then, the germ glands, and there is actually no endocrine tissue in the invertebrate to be directly compared with the internally secreting cells of the vertebrate gonad. The internally secreting mechanism has apparently been added as a new part of the vertebrate gonad and we are as ignorant of its phylogeny or origin from the invertebrate body as we are of the origin of endocrine glands in general.

The gonads in higher vertebrates exert definite effects on structural development during three different periods of life. During embryonic development their secretions seem to regulate in a definite way the formation and growth of the internal and external genital organs. The proof of this statement is beautifully shown by the studies of Lillie and of Tandler on the development of the 'freemartin' calf. When twins of opposite sex are produced in cattle it frequently happens that the two placentae become fused so that the blood from one embryo circulates through the body of the other. Under this condition the male calf develops normally but the development of the gonads becomes arrested in the female twin and the

[1] A part of this paper reports new work that has been done through aid from the Committee for Research on Sex Problems of the National Research Council.

internal and external genitalia of such an individual are abnormal and poorly formed.

After birth there seems to be little activity on the part of the gonads until just before the stage of puberty. At this time their activity increases and the gonadal secretions become important factors in bringing about a fully completed expression of the secondary sex character.

Following this heightened activity at puberty these secretions continue to be very important in influencing the general growth and development of the individual up to the state of complete maturity. There is evidence which would lead us to believe that the gonadal secretions actually influence head shape and the general shape and height of the individual. It is well known, of course, that the eunuch does not present the typical shape and stature of a normal individual. Other well recognized structural changes occur after menopause and during senility, which may be either primarily or indirectly associated with the disappearance of gonadal secretions.

In addition to this general life cycle of varying effects the endocrine tissues of the gonads also show a most pronounced short interval rhythmic activity. No other endocrine gland shows such well marked rhythms. The secretory rhythm of the gonad brings about a corresponding rhythm in the female genital tract and in reproductive activity. The rhythmical occurrence of ovulation in the female is due to the rhythmical changes in the secretions of the gonad.

A final point of distinction between the endocrine tissues of the gonads and the other internally secreting glands is that the gonadal secretions seem more largely associated with reproduction and the preservation of the species, while the other glands are more directly concerned with the preservation of the individual or self-preservation. Removal of the thyroid, adrenals or pancreas will result in great inconvenience or death to the individual, while the removal of gonads does not greatly handicap the individual's welfare but completely does away with the possibility of reproduction.

These complex influences on growth and development and on the general sex rhythm furnish many varied points for attack in attempting to analyze the play of the gonadal secretions. The study of these secretions is a broad, intricate biological problem that must be considered from many angles if it is to be properly analyzed.

We may now briefly review a number of general facts bearing on

the nature and action of the gonadal secretion. One of the methods that has given much insight into the influence of these secretions has been a study of the changes taking place after the removal of the glands.

There has been considerable study of the result of castration in human beings. The eunuchs of the East and the religious sect in Russia known as Scopec have been recently studied by Tandler and Gross and by Martin. The age at which castration is performed is a point of importance in the nature of the structural changes which follow. Typical body changes occur in both males and females after removal of the gonads. In all such individuals the thyroid becomes small and it is claimed that the hypophysis becomes enlarged, particularly in the female after ovariotomy. After castration in lower mammals there is a pronounced degeneration of the seminal vesicles and prostate and of the external genitalia. The human castrate grows tall, the shape of the pelvis is somewhat modified, and the general bone growth takes place as if reacting to a changed condition of growth regulation.

The removal of the gonads from birds produces changes quite comparable to those seen among mammals. In the case of the domestic fowl, the castrated capon shows a very reduced condition of its comb and wattles, while on the other hand, the general plumage of such a bird is developed even beyond the gaudy male pattern. The body weight here increases as it does in the castrated mammal, so that this practice is largely used for commercial purposes. When the ovary is removed from the hen she assumes after the next moult the plumage of a rooster and may grow spurs and actually behave in many ways like the male. If similar operations be performed on ducks the results are very closely the same.

It is of considerable interest to note that the removal of gonads from the mammal causes both sexes to assume a state quite like the usual female type, while the removal of the gonads from birds on the contrary causes both sexes to develop plumage of the usual male type. In both groups, therefore, the characteristics of the operated individual approach in general the homozygous sex which has in its cells the two X-chromosomes instead of one. In the mammals this homozygous two X-chromosome condition is in the female and among the birds it is in the male sex.

Among the invertebrates there are some beautiful examples of sex dimorphism, the male and female being widely different in both

form and color. In some insects the male, for example, may have wing color entirely different from the female, or one sex may be wingless while the other is winged. The removal of the gonad even from the embryo of the invertebrate seems to have no effect whatever on the expression of either body form or color. It is, therefore, probable that there is no internal secretion from the gonad of the invertebrate comparable to that in the vertebrates.

The action of gonadal secretions has been extensively studied by transplantation experiments. We sometimes think of this as being a very modern method, yet John Hunter 165 years ago attempted to transplant the gonads in fowls and apparently succeeded in obtaining slight results. Recently this method has become very popular through the work of Steinach, Sands and many others. There have been feminization and masculinization experiments in which certain body structures were made to change and resemble the opposite sex. Most of these modified characters are those which actually exist in both sexes, such as the mammary gland, hair, size, etc. Definite sex limited structures such as the uterus and tubes in the female and the ducts of the male are not changed over toward the opposite sex. It would seem in general that sex differentiation is not altogether complete or fixed but sex determination in mammals at least seems to be definitely complete and the one sex cannot be changed into the other.

There have been many experiments on the effects of feeding with sex glands but none of these have given clear or reliable results. This would seem to indicate that the secretions of the glands are not effective through the alimentary tract at least in the form administered. The injection of extracts has given more definite results. This again is not an ultra modern practice since Brown Séquard in 1889 injected testicular extracts subcutaneously in man. He believed that effects were obtained. The present results from such injections are probably very little different from his though modern means of exploitation are considerably more advanced. Much work of this nature has been done on lower animals. The results, however, have all been very indefinite, as might readily be expected since there has been no proper method for standardizing the extracts used either on animals or the human being.

Since it seems so certain that both the testis and ovary actually produce important secretions, the question arises as to exactly what cells or tissues in these organs are the important secretory elements.

The case of the testis is simpler than that of the ovary. Here the discussion has been as to whether interstitial cells or the true generative cells produce the secretion. With a pertinent bearing on this question it has been found that a marked eunuchoid type might actually possess perfect spermatozoa while, on the other hand, a perfectly developed male type might have completely degenerate germinal epithelia. Such conditions as these make it seem that the interstitial cells are the important element in bringing about the fully expressed sex characteristics. The action of the embryonic secretion from the testis before there is any active germinal epithelium, as shown in the 'free-martin' studies, is also a case in point. X-ray treatments destroy the germinal epithelium without modifying the body type. The removal of most of the testicular material from the body seems to have no effect—only a small remaining portion of one testis seems sufficient to maintain the normal male body condition. There is no hypertrophy of portions of the testis.

The case of the ovary is more complex. It must not only influence growth conditions but must later regulate uterine rhythm, placentation, and probably other phenomena. In the ovary a number of different kinds of cells have been thought to produce various secretions. There are here interstitial cells believed by many to arise from atretic follicles, follicular cells, cells of the corpora lutea, and the ovum itself. It is very difficult of course to competely separate or isolate the activity of any one of these types in an experimental way. When one ovary is removed the other hypertrophies to a great extent and a small piece of ovary will grow into a whole organ. The single ovary tends to ovulate as abundantly or more so than both ovaries did originally. The ovarian secretions, as pointed out in considering the gonads in general, exert different effects on growth and development at different life periods. The ovary after menopause completely degenerates and yet the individual may live for years with no more rapid ageing after menopause than before the degeneration of the ovary. This fact in itself should make one question whether the lowering of the gonadal secretions is a primary cause of old age rather than one of the symptoms.

The secretions from the male and female gonad have been thought by many to be antagonistic in their actions. In order to test this, adult rats of opposite sex have been artificially grafted together, producing a condition of parabiosis. There was first thought to be antagonistic effects which caused the gonads of both components to

become degenerate but it was later found by several workers that a castrated animal might be fused to a normal animal of the same sex and yet the gonads of the normal animal would tend to degenerate under such a condition. Recently very interesting experiments have been made by Burns at Yale in grafting together tadpoles before the development and differentiation of sex, in order to determine whether one sex in its development might influence the other. It happened that every pair of grafted tadpoles that lived to reach a stage where the sex could be identified were invariably a single sex pair, either two males or two females. In this experiment, either all grafts of opposite sex have died, which seems to me probable, or else it might be that one component in the pair transforms the sex of the other so that both members of the pair are always of the same sex.

It should be remembered in considering all specific hormone effects produced by the gonads that other endocrine glands may very probably be involved. The nervous system is also concerned. The removal of eggs from the nest of a bird may cause a single female to produce as many eggs in forty days as she might have ovulated in five years. This is a definite effect on the ovary through the central nervous system of the bird in reacting to the taking away of her eggs from the nest. In line with this is the fact that menstruation and ovulation may be suppressed by hypnosis in the human female.

The effect of the removal of the thyroid gland on the ovary is well recognized by most physicians, and it is well known that among lower mammals a considerable degeneration of the ovary takes place after removal of the thyroid. Papanicolaou and Bagg in our laboratory have recently found that radium radiation on the thyroid in guinea pigs may cause a hyperactivity of this gland. The ovary in such animals gave a very marked reaction to this thyroid condition. Ovogenesis is greatly activated and the new cells migrate down into the stroma and form new Graafian follicles. There is also a change in the cellular picture of the vaginal smear after radiation of the thyroid and the resulting stimulation of the ovary. This is quite an opposite reaction on the part of the ovary from that which follows the removal of the thyroid gland.

All of the foregoing facts show the importance of the endocrine secretions from the sex glands. Yet all of the phenomena so far discussed are simply qualitative changes resulting from a hit or miss method of experiment, and none of the results discussed are definitely

measureable or quantitative in type. This is necessarily true since up to the present time there has been no definitely established indicator against which the gonadal secretions could be definitely measured or standardized. The results of experiments may be spectacular but they are of little definite value unless quantitatively expressed and subject to accurate repetition. The gonadal hormones must be brought up to some such point of standardization as that obtained for the suprarenal substance and insulin. In order to attain this aim there must be devised some indicator against which these secretions may be accurately measured and tested. For the past eight years Dr. Papanicolaou and I have been studying the ovarian reactions in guinea pigs by using the changes in the uterine and vaginal epithelia as an indicator for the ovarian condition. The action of ovarian hormones on the uterus and vagina are very definite in giving certain cellular expressions which may be accurately recognized.

In making smears from the content of the vagina we first found that the cellular appearance changed in a very exact way in correspondence with the sexual stage of the animal. These observations were controlled by both operations and autopsies so as to establish a definite connection between the appearance of the smear, the condition of the vaginal wall, the uterine wall, and the ovary. These relations have been so clearly analyzed that anyone may examine a smear of the cells from the vagina and know very definitely exactly what the condition of the uterus and ovary are at this time By such a method one is actually able to predict within the hour the exact time of ovulation. These experiments have been repeated by a number of other workers—Long and Evans with the rat, Allen with the mouse, and a number of others using different mammals. In all these animals it is readily possible to definitely diagnose the oestrous stages and to know the exact state of the ovary from examination of the vaginal smear. It now became evident that any treatment or experiment which tended to influence the condition of the ovary might readily be detected by some modification in the vaginal smear. We studied the effect of a number of modified conditions such as starvation and underfeeding and various operations, and found that in certain cases ovulation could be completely suppressed and the vaginal smear would definitely indicate the fact. If ovulation was accelerated this of course could be recognized in the same way. Allen by employing this method was able to detect the effect of the follicular hormone on the uterine reaction of female mice from which

the ovaries had previously been removed. In this way Allen and Doisey have learned many points of importance about the follicular hormone.

A group of us in the laboratory at Cornell have been able to measure very definitely the quality and strength of several ovarian preparations. There has been obtained a definite acceleration of ovulation in the guinea pig by injections of the follicular hormone, and an equally clear-cut delay in ovulation as a result of measured tests of a purified lutean extract. Papanicolaou has recently reported in some detail these findings.

It seems quite evident from the amount of investigation already conducted that the vaginal smear method offers a most accurate indicator for the study of ovarian extracts and of ovarian reactions, and by this method it is believed that the endocrine products of the ovary may be as accurately measured on the basis of unit doses as is now possible in the case of insulin. Certainly much work remains to be done, but it may clearly be followed along these lines.

We have attempted to extend this work to human beings and through co-operation with the Woman's Hospital in New York considerable progress has been attained. Dr. Papanicolaou finds that the various stages of the ovarian cycle in the human may be detected with considerable probability by examination of vaginal smears. The human smear is somewhat more difficult to analyze than that of the lower animals, but with experience it seems perfectly practical to use it as a general indicator. In working with the human cases it has also been found that early stages of pregnancy and other abnormal conditions of the ovary and uterus may be detected by peculiar changes in the picture of the vaginal smear. Papanicolaou has already reported in a brief way the general nature of the modified smear of pregnancy and this study is being actively continued at the present time.

Finally, we are encouraged to hope, in the light of the recent advances which have been made by the use of the vaginal smear method, that much really accurate quantitative knowledge is soon to be obtained regarding the various functions of ovarian secretions. This method of study also gives us a more clear-cut means of detecting the influence of the secretions from other endocrine glands on the ovarian reaction. The relationships between the thyroid and pituitary and the ovary may be further elucidated by our present methods of study.

In concluding I would like to stress the remarkable fact that this morphological indicator is as accurate and clean-cut in its response to chemical changes in the body as is any other type of diagnostic reaction.

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SOME GENERAL FEATURES OF ENDOCRINE INFLUENCE ON METABOLISM.

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A fairly constant or steady state, maintained in many aspects of the bodily economy even when they are beset by conditions tending to disturb them, is a most remarkable characteristic of the living organism. Though the blood is the common carrier for all manner of food material and for waste, its composition varies to a surprisingly slight degree. Though warm-blooded animals are exposed to numerous and extensive alterations of surrounding temperature, they themselves undergo shifts of temperature within only a brief range. And though food is taken in as it is provided or desired and is utilized as conditions may demand, the body weight of the full-grown individual continues for long periods on a strikingly even level. Since in these, and in other instances which could be added to them, circumstances are often present which, if not controlled, would profoundly modify the constancy of the state, we must assume that controlling factors are at hand ready to act whenever the constancy is imperilled. The existence of steady states in the body and some agencies maintaining them have, of course, long been recognized. On this occasion I am laying emphasis upon these states because of an interest in some tentative general considerations with regard to physiological factors regulating them, and in the possible bearing of these considerations on problems of internal secretion. As they may have value in suggesting lines of research and bases for critical judgment, they may be worthy of attention.

Six Propositions Regarding Physiological Factors Maintaining Steady States in the Body.

The first proposition is that in an open system, such as our bodies represent, complex and subject to numberless disturbances, the very existence of a poised or steady state is in itself evidence that agencies are at hand keeping the balance, or ready to act in such a way as to keep the balance. These agencies may act antagonistically, like the nerves of the heart. A tonic action is also possible, as in arterial vasoconstriction, with constancy provided indirectly, one step back,

in a nerve center subjected to opposed control. The regulation may consist of a check on the excesses of a continuous function, like the respiratory setting of the carbon-dioxide level in the blood. Again, there may be limitation by overflow, a safety-valve arrangement, as in the renal thresholds of overflow or escape for various constituents of the blood.

A second proposition is that, if the state remains steady, there is an automatic arrangement whereby any tendency towards change is effectively met by increased action of the factor or factors which resist the change. Somewhat similar statements of this proposal have been made by Spencer (1) and also by the Belgian physiologist Frédéricq (2). They did not recognize, however, failure of the state to retain its poise because of absence or weakness of a controlling agent—a not uncommon consequence of pathological processes. For that reason I have made the statement conditional ("if the state remains steady"). As Lotka (3) has pointed out, such a reservation, which is required for constant states in living beings, and which is a recognition of their lack of permanent stability, would sharply distinguish the proposal from the strict principle of Le Chatelier which was enunciated for physico-chemical systems.

A third proposition is that any factor which operates to maintain a steady state by action in one direction does not act at the same point in the opposite direction. This declaration may appear tautological, but, as will be shown later, it has interesting bearings, and if its probable truth had been recognized, it would have led to more cautious conclusions than have been drawn.

A fourth proposition, related to the third, is that factors which may be antagonistic in one region, where they effect a balance, may be co-operative in another region. It is necessary, therefore, to define closely the field of action of opposing factors in discussing a physiological equilibrium.

A fifth proposition is that the system of checks which determines a balanced state may not be constituted of only two antagonistic factors; on either side there may be two or more, brought into action at the same time or successively. Further, the two may be of different nature, e.g., an internal secretion and a neuromuscular agency.

A sixth proposition is that when a physiological factor is known which can shift a steady state in one direction, it is reasonable to look for a physiological factor or factors having a contrary or counterbalancing effect.

In the foregoing statements the expression "ready to act" has been used as an alternative to "acting" because in certain instances there is evidence that the situation is not kept balanced by direct and immediate opposition of active agencies, but is allowed to move to and fro within limits or within critical points, possibly under control of simple physico-chemical adjustments, and only when these limits are passed are the more complex and indirect physiological agencies (i.e., those involving reactions peculiar to the organization of living beings) brought into play.

The advances in our knowledge of the relations of internal secretion to metabolism have lately been so great and so various that an attempt to present an encyclopedic survey in brief compass would be futile. Instead, may we not consider the six propositions, stated above, with regard to some recent investigations and results, and see to what degree interpretation is clarified thereby and new lines of work are indicated. In doing so I wish to disclaim any effort at an elaborate or final scheme of relationships. The concept of equilibrating factors will be used merely as a means of unifying some apparently diverse and separate observations which, in the main, have been personal experiences.

The Equilibrating Factors in the Blood-Sugar Balance.

Carbohydrate is the material most readily burned in the body. When it is provided in abundance, the combustion of fat is almost completely stopped and the combustion of protein is reduced to a minimum. In less than a half-hour after the ingestion of sugar the respiratory quotient usually rises to about 1.0 (4). The concurrent testimony of investigators supports the conclusion that carbohydrate is not only the most readily utilizable source of energy, but is essential for working the mechanism of muscular contraction. Its importance, therefore, need not be emphasized.

In the economics of the body, problems arise concerning carbohydrate demand and supply because that foodstuff is continuously being used up and is renewed only periodically. When it is taken in and is being digested it must not be permitted to increase in the blood above 170 or 180 mg. per 100 cc., for then it will be lost by escape through the kidneys. The amount available is likely to be more than is needed for current uses; the excess must be set aside in storage, in a compact and not immediately utilizable form. This is

accomplished chiefly in the liver, though there are, of course, the scattered local stores. When need arises the stored carbohydrate must be released from the liver, for if the glucose in the blood falls to approximately 45 mg. convulsions are likely to occur, which may be followed by coma and death. Thus, in sum, the blood-sugar level is an equilibrium between the supply and the demand, with storage as an adjusting arrangement. The normal outer limits of the equilibrium may be regarded as at approximately 180 mg. where loss occurs, and approximately 45 mg. where convulsions occur. But the normal variations of blood sugar are ordinarily well within these extreme limits. If our earlier propositions are correct, factors are at work holding the oscillations inside the narrower confines. Some recent work, done by McIver and Bliss and myself (5), has revealed a sympathico-adrenal mechanism as one factor in the balance, protecting the body against the dangers of too low blood sugar.

As an indicator of increased adrenal secretion we have used the heart, disconnected from the central nervous system and left in the body to perform its function. If the temperature is kept normal, only changes in the blood stream can affect the rate. Alterations of blood pressure do not influence it, but a very slight increase in the adrenin content of the blood promptly makes the heart beat faster. Anrep and Daly (6) have recently found that the denervated heart is sensitive to the presence of adrenin, 1 part in 1,400 million parts of blood. All investigators now admit that medulliadrenal secretion is controlled by sympathetic impulses. Afferent stimulation and asphyxia, which are known to discharge sympathetic impulses, cause acceleration of the denervated heart—just such a change as is produced by increase of adrenin in the blood. The only agent which may confuse the response in an acute experiment is a substance given off from the liver after protein feeding—a source of trouble which can be made insignificant by study of a fasting animal or abolished by severing the hepatic nerves (7). If these precautions are taken the positive response disappears when the adrenal glands are removed or inactivated by nerve section. The faster heart rate, therefore, is then due to medulliadrenal secretion (8). The results which we have obtained by use of the denervated heart have been questioned by Stewart and Rogoff (9). These results, however, have been confirmed by Tournade and Chabrol (10) in Algiers, working with a crossed circulation; by Houssay and Molinelli (11) in Buenos Aires, also employing a crossed circulation; by Florovsky

(12) and by Baschmakoff (13) in Kasan, using the denervated salivary gland; by Hartman, McCordock and Loder (14) in Buffalo, recording the reactions of the completely denervated iris; and by Anrep (15, 16) in London, studying the denervated heart and kidney and also the isolated heart outside the body but connected with the abdominal aorta and inferior vena cava. Furthermore, Kodama (16) in Sendai, Japan, repeating the procedure of Stewart and Rogoff, has found, not what they found, but what we found. Naturally Stewart and Rogoff have criticised Kodama's results and have declared that he did not master their technique (17). A recent letter from Sendai, however, states that other workers there have refined the method, and that Kodama's data have been fully substantiated. If any investigator anywhere had given Stewart and Rogoff any support for their contention that adrenal secretion is constant, and unaffected by conditions which induce sympathetic activity, there might be reason for seriously considering it. But that support is lacking. Opposed to it is the concordant experience of other investigators, derived from a variety of methods. It justifies confidence in the result obtained by use of the denervated heart as a signal for greater discharge from the adrenal medulla.

Now to return to the question of a sympathico-adrenal factor working to keep the blood sugar normal and to protect the organism from dangerous hypoglycemia. Among the hypoglycemic reactions which occur when an excessive dose of insulin has been given are pallor, a rapid pulse, dilatation of the pupils and profuse sweating. These are phenomena resulting from sympathetic impulses. The denervated heart tells whether the adrenal medulla shares in this increased activity. When, after an injection of insulin, the glycemic concentration is falling, it reaches a critical point at which the denervated heart begins to beat faster. And as the sugar percentage continues to fall the heart rate continues to rise until a maximum is reached. In the unanesthetized test animal the critical point lies between 70 and 80 mg. of glucose per 100 c.c. of blood—a concentration at which in man also hypoglycemic symptoms first appear (18). The faster beating of the denervated heart indicates that medulliadrenal secretion has been stimulated. That inference is verified by removal of the glands, or by removal of one and denervation of the other, whereupon a fall of the glycemic percentage below the critical point is not accompanied by a more rapid heart beat. The faster beating of the heart, of course, indicates that impulses are

being discharged along splanchnic fibres. These sympathetic impulses, in co-operation with increased adrenal secretion, might be expected to call forth sugar from the liver. This inference is confirmed by the fact that as the rate of the denervated heart increases (manifesting sympathico-adrenal activity), the rate of falling of the glycemic percentage is checked. And if not too much insulin has been given, the glycemic percentage may not only cease dropping, but may rise to normal. A highly significant feature of this sympathico-adrenal activity is that as the blood-sugar level rises the activity subsides. Indeed, when glucose is injected intravenously the activity has been seen to subside completely within two minutes.

Here is a remarkable mechanism having the function of keeping up the physiological percentage of blood sugar when there is danger of deficiency. After a dose of insulin the mechanism may be brought into service hours before a convulsion occurs, and if effective it may wholly protect against a convulsion. From the evidence provided by these observations we may conclude that the lower inner limit of variation of blood sugar, when the sugar is being reduced, lies in the region of 70-80 mg. Reduction below this limit calls into action a sympathico-adrenal factor working to prevent further reduction. This factor works with increasing vigor the lower the glycemic percentage, until an acme is reached in a convulsion when the denervated heart beats most rapidly.

According to Olmsted and Logan (20) the convulsive seizures do not occur in a spinal animal, even when the glycemic percentage is extremely reduced. The sensitive region appears to be in the medulla or midbrain, for in decerebrate animals typical convulsions result from hypoglycemia. Rapport and I (21) have shown that a center for medulliadrenal secretion exists in the fore part of the floor of the fourth ventricle. Quite possibly this region is especially sensitive to a reduced sugar supply and by sympathico-adrenal discharges (culminating in spasms) protects the rest of the body against the hazards of too great a reduction.

Our results have received support from Abe (22) who made use of the sensitized iris to signal a greater output from the adrenal medulla. In some instances he noted no effect, or very slight effect, during the first half-hour after giving insulin. Then there was a sudden change, marking the onset of the sympathico-adrenal function as the blood-sugar percentage fell. Houssay, Lewis and Molinelli (23) also have supported our conclusions. They employed

a crossed circulation from the left adrenal vein of one dog to a jugular vein of another. When an insulin hypoglycemia was established in the donor, hyperglycemia was produced in the recipient—a result which did not occur if the left splanchnics of the donor had previously been severed. Both methods showed that adrenal secretion was increased by hypoglycemia, but unfortunately they were not used in such a way as to bring out the evidence for the critical point at which the sympathico-adrenal mechanism is set going, an observation of special interest in relation to the glycemic equilibrium.

In our second proposition we postulated that the preservation of a balanced state implies an automatic arrangement whereby a tendency to change is met by increased action of a factor or factors which resist the change. We have surveyed the evidence for a factor checking a shift of the glycemic equilibrium downwards. What agency or agencies operate in the opposite sense, to prevent a shift upwards, towards a high sugar concentration? The answer might be given promptly that it is the internal secretion of the pancreas, if competent investigators had not concluded that insulin administered to normal animals is capable of decreasing hepatic glycogen, i.e., that insulin may work in the same direction with the sympathico-adrenal mechanism. There is excellent reason for believing, however, that insulin primarily is the opposing factor and that its apparently anomalous effect in normal animals should be regarded as a secondary phenomenon. Let us examine the basis for the inference that the internal secretion of the pancreas, or insulin, normally protects the body against hyperglycemia by promoting sugar storage in the liver.

First, there is the outstanding fact that removal of the pancreas is promptly followed by hyperglycemia and a great reduction in the hepatic glycogen reserve. This phenomenon is so well known as to need no emphasis. Secondly, as Banting and his collaborators (24) have shown, the administration of insulin to depancreatized animals not only brings the blood sugar down to the normal level, but causes glycogen to accumulate again in large amounts in the hepatic cells. Indeed the hepatic glycogen of insulin-treated diabetic animals may be considerably more than in normal well-fed controls. Again, it has been found that insulin will induce a deposit of glycogen in the liver when the blood sugar is within the range of normal variations. Thus, Cori (25) has recently reported that the amount of

hepatic glycogen may be quadrupled in phlorizinized rabbits by repeated doses of insulin. Finally, as bearing on the antagonism between the glycogenolytic action of adrenin and the glycogenetic action of insulin, there may be cited the experiments of McCormick, Noble and O'Brien (26). They discovered that when large doses of adrenalin were injected—doses which produced a marked reduction of hepatic glycogen in control animals—the additional injection of insulin was accompanied by a striking retention of the hepatic glycogen. The excessive doses of adrenalin used by them (e.g., 2.5 c.c. in a rabbit) allowed, they state, "enormous quantities of insulin" (e.g., 140 units) to be tolerated without convulsions. All these various observations bear witness to the importance of the internal secretion of the pancreas (insulin) as an agent operating conversely to the sympathico-adrenal mechanism in affecting the glycemic percentage by action on the liver.

The suggestion that insulin does not act in one direction only but in both directions on the liver (i.e., glycogenetically and glycogenolytically) has, to be sure, been derived from experiments on normal animals. McCormick and Macleod (27) gave insulin and carbohydrates to rabbits rendered free of glycogen and found that less glycogen was deposited in the livers of the insulin-treated animals. Dudley and Marrian (28) compared the livers of glycogen-rich mice and rabbits, some of which had received insulin and others left as controls; the hepatic glycogen of the former was very greatly reduced as compared with the latter. Babkin (29) also has reported that the glycogen content of the liver in well-nourished rabbits which had been given insulin is markedly lowered. The comments on these experiments have been somewhat equivocal. Thus Macleod (30) states that "there can be no doubt that insulin causes a rapid reduction in the amount of glycogen in the liver," but he also remarks later that at some stage after the blood sugar has become reduced by insulin "the glycogenolytic process in the liver is stimulated." A similar suggestion was offered by Dudley and Marrian. In our third proposition we intimated that a factor does not have such opposed functions with reference to the equilibrium which it protects. If we keep that idea in mind and remember that hypoglycemia calls forth sympathico-adrenal service, the results above detailed can be reasonably explained. It is significant that in the experiments of McCormick and Macleod, despite an effort to give doses of insulin "just insufficient to cause convulsions," convulsions occurred

in 6 out of 15 cases; in the experiments of Dudley and Marrian the animals were killed on the appearance of convulsions; and in the experiments of Babkin, though "convulsions were not observed," the glycemic percentage was far below the critical level. In all these experiments, therefore, the conditions were such that the hepatic glycogen stores were being drawn upon, not by direct action of insulin, but by the direct action of the factor opposed to insulin—the sympathico-adrenal factor—made to operate powerfully by the insulin hypoglycemia. This conclusion is supported by the testimony of Burn (31) that a small dose of insulin, mildly effective in the normal animal, causes in an animal treated with ergotamine profound hypoglycemia, with convulsions and collapse; for ergotamine, though having no influence on the action of insulin, paralyses the protective sympathico-adrenal reaction. That the secreted adrenin plays an important part in this reaction is proved by the fact that the fall of the glycemic percentage is not checked, or is only slightly checked, at the critical point, if the adrenals have previously been inactivated (5), and also under such conditions by the appearance of convulsions sooner and after smaller doses of insulin than in animals with active glands—a phenomenon observed by Sundberg (32), by Lewis (33), and by us (5).

From all the foregoing evidence it appears that the normal level of blood sugar is preserved by the sympathico-adrenal factor acting on the low side of the equilibrium and by the pancreatic factor and the renal overflow acting on the high side. Much still remains to be learned regarding the conditions bringing the islands of Langerhans into play. From the experiments of Banting and Gairns (34) the inference may be drawn that a nervous control of insulin secretion is not necessary. That does not prove, however, that nervous control does not exist and could not be useful—the innervation of the heart is not *necessary!* The observations of De Corral (35) and of McCormick, Macleod and O'Brien (36) point to vagus impulses as causing a discharge of insulin into the blood stream. Recent (unpublished) studies by Britton at the Harvard Physiological Laboratory, as well as the investigations of Clark (37), have corroborated the earlier evidence. In harmony with these results are those announced by Lewis and Magenta (38) that after section of the abdominal vagi a given dose of insulin is less effective than before. Because in the presence of high glycemic percentages remnants of the pancreas degenerate (39) and the islet cells show signs of over-

work (40), it seems probable that just as the adrenals are stimulated by hypoglycemia, so likewise the "islands" are stimulated by hyperglycemia, i.e., that each secretion is involved in a righting response which restores the normal equilibrium. If further research proves that the vagus provides a fine adjustment for insulin secretion, as the sympathetic does for adrenal secretion, it will be peculiarly interesting because of the common opposition between vagal and sympathetic functions.

A caution appears to be necessary here lest the ideas just expressed be taken as confirming Zuelzer's theory of the adrenal origin of diabetes. Indeed Stewart (42) has declared that my interpretation of the sympathico-adrenal service in maintaining the normal glycemic concentration is only an elaboration of that theory. The essence of Zuelzer's theory was that the adrenals and the pancreas are such aggressive antagonists that when the pancreas is removed diabetes follows because of the unchecked action of the adrenals. The theory has no sound basis. And our observations, that sympathico-adrenal activity, roused by hypoglycemia, is promptly checked by hyperglycemia, and that it is made to work again only when the blood sugar has *fallen* well below the usual level, should have prevented anybody from imagining that our experiments in any sense support Zuelzer's idea. Instead, they raise the question whether the high sugar level of diabetes may not be associated with a depression of sympathico-adrenal function.

It will be recalled that in our fifth proposition we suggested that when opposed factors assure an equilibrium there may be more than one on either side. Indeed, a primary action of the islands of Langerhans and the co-operative overflow arrangement in the kidneys may be regarded as a double device preventing a rise in the glycemic level. On the other arm of the balance may be placed the testimony of Olmsted and Logan (20) that the pituitary body is important. They state that typical convulsive seizures occur in decerebrate animals if the pituitary body has been removed, but that otherwise even massive doses of insulin fail to lower blood sugar to a marked degree. This result has been associated with the observation by Burn (31) that pituitrin can lessen or entirely prevent insulin hypoglycemia. The conclusion that the posterior lobe of the pituitary may collaborate with the adrenal medulla thus seems justified. In a recent investigation, however, Bulatao and I (43) have shown that in decorticated animals with intact pituitary glands insulin

regularly causes a drop in the glycemic concentration, and we have called attention to the same phenomenon in three similar cases described by Olmsted and Logan. Furthermore, we showed that in decorticated and decerebrated animals sympathico-adrenal activity may be maximal and may therefore retard or lessen the effect of insulin. For Olmsted and Logan to conclude on the basis of their few cases, which are not decisive, that the high blood sugar after decerebration is maintained by pituitary influence, seems to us unwarranted. In other words, though pituitrin as a pharmacodynamic agent inhibits the action of insulin, proof is still lacking that a pituitary secretion as such has that effect, and could co-operate with adrenal secretion.

Because of the effects which hypothyroidism, hyperthyroidism and thyroid feeding have in disturbing the glycogen content of the liver and influencing sugar tolerance (44), and also because of reported hypersensitiveness of thyroidectomized animals to insulin (45), it may be that the thyroid normally collaborates with the sympathico-adrenal apparatus. The evidence on this point is still too vague and uncertain, however, to justify discussion of it in this paper.

In our fourth proposition we mentioned that factors opposed in one region of the body may be collaborators in another region. This is perhaps the case with adrenin and insulin. They are opposed with respect to glycogen storage in the liver. They may be collaborators, however, in the utilization of sugar in muscles. Various investigators have found that injected adrenalin accelerates metabolism (46), and recent Harvard studies have proved that secreted adrenin has the same effect (47), and that the effect occurs when the circulation is almost wholly confined to muscles (not yet published). Adrenalin causes in the isolated heart not only a greater consumption of oxygen per unit of time but also may cause total disappearance of the stored glycogen (48). Hepburn and Latchford (49) observed that insulin accelerates removal of glucose from the perfusing fluid by the isolated mammalian heart, and Burn and Dale (50) noted that insulin causes rapid removal of glucose in a decapitated and eviscerated preparation, i.e., when the heart and skeletal muscles are the only important metabolizing organs. The early stages of insulin action in such a preparation are characterized by increased oxygen consumption, with a respiratory quotient of unity. Thus insulin and adrenalin, antagonists in the liver, appear to be collaborators elsewhere. Insulin may promote everywhere the pas-

sage of sugar from the blood into cells. In muscle cells adrenal secretion may work with insulin to facilitate the chemical changes underlying contraction. All this, however, remains to be proved. The suggestion is mentioned here merely to illustrate the possibility of different relations of physiological agents at different places in the organism.

Some Hints at Factors Affecting Protein Equilibria.

Protein is quite as important as carbohydrate for bodily welfare and function. It is necessary for such invaluable services as building the cellular structure of the organism, repairing or restoring the worn or wasted parts, and providing the essentials for coagulation and for normal composition of the blood. It is constantly being disintegrated and lost from the body, and the possibility of securing a new supply is not always at hand. Since there is an elaborate arrangement for storing excess of carbohydrate and for liberating it as required, it would appear reasonable to look for a similar arrangement for storing indispensable protein against a time of need. The process of deaminization and the excretion of extra nitrogen indicate that accumulation of protein must be limited. The existence of a nitrogen equilibrium, capable of being altered and adapted to the requirements of the organism, implies that there prevails an orderly regulation for riddance or retention and the maintenance of a steady state.

The reality of a reserve or "deposit" protein has often been debated. Gradually there has developed a considerable body of evidence that with abundant protein feeding the hepatic cells can store protein just as they can store glycogen. More than forty years ago Afanassiew (51) noted that if "albuminates" were fed to dogs the liver became firm and resistant, and the hepatic cells increased in size and contained between their protoplasmic strands many fine sharply outlined granules, protein in nature. Seitz (52) brought further support, finding that in fed animals the total nitrogen of the liver in relation to that of the rest of the body was from 2 to 3 times as great as in fasting animals. The observations of Berg (53) have been especially significant. In 1914 he reported that in the hepatic cells of animals which are given protein there appear numerous small droplets or masses which are clearly distinguishable from the cell structure, which react as protein to Millon's reagent, which

are caused to disappear by fasting, and which are restored only when protein or amino acids are fed. In 1922 he showed that these droplets can be distinguished in fresh, teased-out liver cells stained with neutral red, and that they give the ninhydrin reaction of the simpler proteins. Berg's earlier observations have been fully confirmed by Stübel (54) and by Noel (55). This histological evidence for a protein reserve has been corroborated by Tichmeneff's chemical studies (56). He starved mice for two days, then killed half of them and, after giving the others an abundance of cooked meat, killed them and compared the livers of the two groups. Expressed in percentage of body weight the livers of the meat-fed animal had increased about 20 per cent, with the hepatic nitrogen content augmented between 53 and 78 per cent.

The concept of storage of valuable material involves the idea not of miserliness but of service—the appropriate use of the material outside the storage place. There appears to be at present no proof that protein is taken from the liver for use in another part of the body which requires restoration or improvement, though the possibility that such a transfer could occur would justify an attempt to search for it. There is testimony, however, to a function which the liver performs in maintaining the protein constituents of the blood. Kerr, Hurwitz and Whipple (57) found that after depletion of blood plasma (by bleedings and injections of washed blood corpuscles in Locke's solution) the restoration of the serum protein is delayed if the liver has been damaged or has been side-tracked by an Eck fistula. Furthermore, liver injury is associated with a fall in the serum proteins. Although in the blood of the normal animal fibrinogen is rapidly reformed after being removed, Meek found that it fails to be reformed if the liver is unable to act (58). It seems, therefore, that the liver plays a fundamental rôle in the production of fibrinogen. In the production of antithrombin or antiprothrombin as well, and possibly of heparin also, there are indications that the liver is concerned and thereby might influence deeply the coagulation of the blood.

The serum proteins remain at a remarkably steady concentration, fluctuating only slightly with fasting, feeding, health or disease. And yet, as shown above, when they are reduced, the liver soon restores them. Again, the factors concerned with blood clotting are ordinarily in balance, so that coagulation takes a moderate and fairly uniform time. The relations can be disturbed, however, so

that the time is longer or shorter. In experiments by Gray and myself (59) we obtained records of a shortening of the clotting time of blood by adrenalin injections if the blood is allowed to circulate through abdominal organs; the phenomenon fails if the circulation is confined above the diaphragm or if the intestines and liver have been removed. Increased adrenal secretion induced by splanchnic stimulation or excitement has a similar effect, as shown by experiments done in co-operation with Mendenhall (60). According to Grabfield (61) adrenalin increases the prothrombin element in the blood. It is significant that blood taken at the height of the hypoglycemic reaction, when sympathico-adrenal activity is maximal, "clots almost immediately it is withdrawn," as Macleod (30) has remarked, and as we have also noted. Finally, as Gray and Lunt (62) showed, a large hemorrhage hastens the coagulation of blood if the liver (and intestine) are in the circulation, but not if the blood flow is excluded from the abdomen. Since the sympathetic is stimulated by considerable hemorrhage, probably sympathico-adrenal action is normally involved in the response.

Additional evidence that the protein material of the liver can be called out by appropriate stimulation was furnished by Stübel (54) who found that the deposited droplets or small masses in the hepatic cells could be greatly reduced by injecting adrenalin subcutaneously. Moreover, in collaboration with Uridil and with Griffith (63), we have shown that after protein feeding, stimulation of the nerves of the liver causes discharge of a still undetermined substance which accelerates the heart and causes a noteworthy increase of arterial pressure. The phenomenon is reduced to insignificance in animals which have been fasting, or which have been fed carbohydrate or fat.

From the foregoing observations we may conclude that the liver is an organ of central importance not only for carbohydrate, but also for protein metabolism. It shares with other parts the power of constructing protein from amino acids, but when large amounts of protein are fed it lays by a reserve or deposit to a much greater degree than do the other parts (56). This reserve can be called out by sympathetic stimulation and by adrenin. In maintaining the normal consistency and coagulability of the blood the liver is indispensable. Here are steady states in which the liver performs quite as important a task as it performs in the carbohydrate balance of the body, and probably the factors which control the situation act with quite as great a degree of nicety. Unfortunately we are still in a

twilight zone which surrounds the problem, and vision is not clear. Hints have been given as to factors affecting the protein levels, but much work must still be done before we shall be well informed regarding them or their ways of producing steady states.

An Endocrine Factor Operating to Maintain the Temperature Equilibrium.

The uniform temperature of warm-blooded animals, though they are exposed to very different environmental temperatures, has already been alluded to as an outstanding example of physiological constancy. The temperature equilibrium is maintained by opposing factors. Concerning the nature of the physical factors, vasodilation and sweating, which operate when the body temperature tends to rise, there has been no difference of opinion. On the other hand, factors which are set in action when the temperature tends to fall have been the subject of discussion for more than a third of a century. Speck (64), Loewy (65), Johansson (66) and Sjöström (67) have concluded, from experiments in which subjects were exposed to cold surroundings, that the increased metabolism which results is to be explained wholly in terms of shivering or other muscular contraction. Voit (68), Rubner (69) and recently Leonard Hill and his co-workers (70), on the contrary, have conducted experiments in which subjects were similarly exposed to cold surroundings, but usually for long periods, and have found acceleration of the metabolic rate with no demonstrable muscular movements. "It is incomprehensible," Rubner wrote, "that many physiologists can still doubt the presence of this powerful regulating mechanism. And it is just as incomprehensible that the increase of heat in the presence of cold is ascribed solely to the gross shivering of the animal." What the nature of the chemical regulator is he did not suggest.

When warm-blooded animals are exposed to cold the striking reactions are erection of hairs or ruffling of feathers, constriction of peripheral vessels and increase of blood sugar. These are signs that the sympathetic division of the autonomic system is in action. Is secretion from the adrenal medulla augmented under these conditions? The answer to this question has interesting bearings on the old controversy regarding chemical control of body temperature. Since 1906 various observers have found that adrenalin stimulates oxygen consumption in isolated organs or in the body as a whole.

This pharmacological evidence was given a physiological significance when Aub, Forman and Bright (71), at the Harvard Physiological Laboratory, found that if the adrenal glands are removed, though blood pressure and the body temperature remain unchanged, the metabolic rate may drop as much as 25 per cent below the previous normal level, and when later McIver and Bright (47) demonstrated that increased adrenal secretion accelerates the oxidative processes of the body. Clearly, if cold excites a greater outpouring of adrenin into the blood stream, it would induce a faster burning in the body just when there would be need for it.

Cramer (72) and Fujii (73) have reported reduction of the chromaffine substance of the adrenal medulla in animals exposed to low temperatures, but that condition, as Trendelenburg (74) has suggested, may not have resulted from over-discharge but from under-production. More direct evidence of an increased medulliadrenal secretion brought on by cooling was obtained by Hartman and his collaborators (75). Using the completely denervated iris of the cat to signal greater discharge of adrenin, they observed that dilatation of the pupil resulted when the cats were dipped in cold water or when they were dipped in warm water and while wet were placed in a cold room or exposed to a current of cool air. The dilatation failed to occur if the adrenal glands were removed or inactivated. The use of the iris by Hartman has been severely criticised by Stewart and Rogoff (76), who, however, have not used the completely denervated structure themselves, and who have, therefore, no good basis for judgment. Because Hartman's results have been doubted and also because we desired to eliminate quite certainly any emotional element (which wetting may have aroused in the cat), Querido and I (77) have investigated the reaction by other methods.

As is other experiments, we have employed the denervated heart as an indicator of augmented adrenal secretion. We tried several different modes of exposing animals to cold before we hit upon the one which proved most satisfactory—that of introducing into the stomach a known amount of ice-cold water. The body heat of the animal passes into the cold fluid, and, unless the temperature is to fall, heat production must be increased to compensate for the loss. We have called the situation confronting the organism under the circumstances its "heat liability." Obviously, since the weight, the temperature and the specific heat of the water are known, the number of calories which the animal must conserve or produce or both,

in order to prevent a temperature fall, can be calculated and nicely adjusted to the purposes of the experiment.

When heat liabilities varying between 1,050 and 2,400 small calories per kilo were established there were invariably faster rates of the denervated heart, ranging from 15 to 64 per cent increase. When the adrenal glands were inactivated and similar heat liabilities were presented to the organism the increases ranged between 2 and 6 per cent only. And if, instead of ice-cold water, water near the body temperature was used the percentage increase was negligible. Since cold slows the rate of the isolated heart, the faster rate which follows the introduction of cold water occurs in spite of adverse conditions, a true physiological response. And since this response fails when the adrenal glands are not acting, the inference is justified that the faster heart rate is a consequence of greater adrenal secretion.

If the heat liability is more than 1,000 calories per kilo, acceleration of the denervated heart is almost uniformly attended by shivering. Thus, two calorigenic factors, secreted adrenin and muscular movements, are co-operating to protect against a shift of the temperature equilibrium towards the low side. But the shivering factor is not an essential part of the reaction, for if a heat liability of only 900 calories per kilo is to be met, shivering rarely occurs; and if it occurs, it is of short duration. The heart rate is faster, however, showing that the adrenal factor is operating.

The increase of adrenal secretion when the organism is exposed to the danger of too rapid heat loss, and the ability of naturally secreted adrenin to accelerate heat production, point to a physiological reaction the services of which to the organism ought to be demonstrable. To test the capacity of this reaction we have studied the effect of a certain heat liability on shivering when the adrenal glands were active or inactive, and we have observed the influence of heat liability on the metabolic rate in the absence of shivering.

I have already remarked that if a heat liability of 900 calories is presented to the organism (cat), shivering rarely occurs or is brief. In 15 cases shivering occurred only twice and lasted in each instance only 3 minutes. In 15 cases in which the adrenals were inactivated by removal of one gland and denervation of the other, the same heat liability per kilo caused shivering in 13, and furthermore, the shivering usually lasted considerably longer than in the control series—for 6, 7, 8, 11, 13 and even 16 and 17 minutes instead of 3 minutes. Thus the primary protection against a heat deficit in the body is

found in activities of the sympathetic system (erection of hairs, vasoconstriction, liberation of easily combustible sugar, and discharge of adrenin), for these responses occur before shivering occurs and may be the only manifestation of the influence of a heat liability. If animals have been deprived of the calorigenic service of the adrenal medulla, however, greater demands are made on muscular activity as a means of maintaining the normal temperature. Under normal conditions, therefore, two lines of defense are erected against a shift of the temperature equilibrium towards the low side. The first line is the sympathico-adrenal mechanism; if that fails and the temperature tends to drop in spite of it, the second line, muscular action or shivering, is invoked to produce the needed heat. And just as the convulsive seizures in hypoglycemia are attended by a greater adrenal discharge, so likewise is shivering due to cold thus attended. In both circumstances the introduction of the muscular factors marks a climax of the action of the automatic arrangements for defense.

If the foregoing inferences are correct, it should be possible to demonstrate a faster metabolic rate in response to a bodily need for heat, quite apart from any muscular quiverings or contractions. To secure evidence on this point Querido and I, and later Bright, Britton and I, have studied the change in the metabolic rate in human beings when a known heat liability was created by taking ice-cold water or that combined with ice. We have now 19 satisfactory observations on 12 different subjects. The heat liability ranged from 360 to 512 small calories per kilo. The metabolic rate has increased in these cases as much as 35 per cent, though the usual increase was not more than 17 per cent, and this without any sign of shivering either objective or subjective. Commonly the first effect of taking the cold water is a drop in metabolism, which is followed by the rise, which reaches its maximum at periods averaging 25 minutes after the liability was established.

The observations described above have direct bearing on the old controversy regarding the nature of the chemical agencies which help to preserve the temperature equilibrium of warm-blooded animals. Careful examination of the records of the experimenters who have argued that muscular contraction alone is the source of needed heat shows that they reported substantial increases of metabolism unattended by shivering. Furthermore, they failed to recognize that shivering may co-exist with and effectively mask a true chemical

calorigenesis. And finally they have inferred that because a chemical mechanism did not operate in certain short experiments the mechanism does not exist—an inference having slight value when confronted by good evidence to the contrary. The results of our experiments are definitely opposed to the idea that a single factor, the muscular factor, is relied upon to keep the temperature balance from tipping downward. They bring support to the testimony and the argument of Voit and of Rubner, and offer an explanation of the chemical regulatory device which they postulated.

The evidence which has just been presented is not to be taken as excluding still other co-operating agencies. The fact that thyroid activity accelerates metabolism, that thyroid removal lowers the metabolic rate and renders one more sensitive to cold, that the thyroid gland is probably subject to sympathetic control (78), that it enlarges in animals exposed to low temperatures (79), that in the compensatory hypertrophy of a remnant the evidences of hyperactivity are greater if the animal is exposed to frigid surroundings (80)—all these observations are highly significant of possible sympathicothyroid collaboration in the upkeep of body temperature. As Aub (81) has suggested, the sympathico-adrenal service may be employed for quick action and the thyroid may act in the same direction, but for more enduring needs. But here we must have more facts before we are warranted in giving thyroid function definitely a place among the compensatory factors evoked by a threatened shift in the temperature equilibrium.

In the foregoing discussion I have used to a large extent the results obtained in personal investigations. This emphasis will not, I trust, be interpreted as implying an over-valuation of the subjects studied or of the results achieved. It seemed best to rely on first-hand experience rather than to summarize the work of others. Furthermore, I wished to illustrate the interest which is added to a search for new facts if certain general ideas are allowed to suggest the direction of the experimenter's imagination and his efforts at securing insight.

In stating the first of the six propositions, i.e., that a steady condition in the body implies physiological agencies serving to maintain it, I mentioned several types. The type of opposed agencies has been illustrated by the operation of the sympathico-adrenal and the probable vago-insular mechanisms in keeping normal the blood-sugar level, and also by the regulation of the temperature equilibrium

by physical and endocrine factors. The outflow or escape type has been illustrated by the function of the kidneys when there is too great a rise in the glycemic percentage. Questions at once appear as to other constant metabolic states, such as the storage and disposal of nitrogen, the laying by of fat, and the constancy of the organic and mineral constituents of the blood. In all these equilibria what agents are at work to limit the variations? What types do they represent? Though there are hints of answers to these questions, reliable information must still be sought.

The second proposition, it will be recalled, postulated corrective activity whenever an equilibrium is disturbed. This service was rendered, as we have seen, by the sympathico-adrenal apparatus in the presence of both hypoglycemia and hypothermia. If this second proposition is generally true, not only must we look for agents which protect a steady state from serious disturbance, but also we must search for the control which makes them act with greater vigor, the more serious the disturbance. Related to this adjusted response is the fifth proposition; that accessory protective functions may be expected to co-operate if the primary functions fail. We have seen this situation in the co-operative activity of the kidney and the pancreas in resisting hyperglycemia; we have seen it also in the vaso-constriction, the increased adrenal secretion and the shivering which constitute progressively the three lines of defense against a drop in the temperature level of the body. We should keep our minds alert, therefore, not only for regulators of steady states, but for the government of the regulators, and for the combination of regulators working towards the same end.

A general inquiry, important for clear understanding of body organization, would be one directed towards determining, so far as possible, the primary or immediate agencies, as contrasted with the secondary agencies, which induce a change of state. For example, we have seen that sympathico-adrenal stimulation is an immediate cause of glycogenolysis. Obviously any other condition inducing glycogenolysis may act, not directly on the liver, but through the sympathetic approach. Until the primary factors are known and properly recognized, we are sure to have confusion—such confusion as is implied in the idea that a corrective agent operates in both directions at the same point.

In my opinion an attempt at present to develop an elaborate and

intricate conception of the interrelations of the endocrine glands would be altogether too premature and might be quite misleading. The necessary facts are not at hand. But the idea that endocrine factors play an important rôle in establishing and maintaining physiological equilibria is reasonable and moderate in its scope, and does not involve a far-reaching projection of theory into the unknown. That the idea has value not only in raising questions regarding the existence and nature of balanced states but also in suggesting ways in which endocrine agencies may affect these states has, I hope, been made evident by the instances which I have cited.

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Discussion of Above Papers.

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In this symposium we have had the privilege of listening to three men, each of whom is a master in his special field, although all are at present working in the general domain of endocrinology and metabolism.

Dr. Abel has given us a lucid account of the general principles that underlie hormonal activities. Dr. Stockard has shown us by his keen analysis of the work on sex glands that there is really something in that subject, although many writers would have us think that there is nothing. A strange *pudor* surrounds questions in the sex domain, even among medical men; one is given the impression that medical men should be "protected" from sex topics as carefully as the pre-adolescent school girl! Dr. Stockard's frank and free discussion of the subject this afternoon was as exhilarating as it was unusual. Dr. Cannon has discussed the maintenance of equilibrium in the body and the relation of endocrine factors to such "steady states." I was glad to hear Dr. Cannon make use of certain general ideas or propositions. Clinicians are all too prone to consider such use as "too hypothetical" or "too speculative," One often hears it said that there should be no hypotheses and no theories in endocrinology—only facts. There is nothing more erroneous than such an idea. To acquire facts, one must first work according to some theory or hypothesis. On the other hand, one should know *when* he is speculating. The great harm comes from assuming that hypothetical constructions are established principles; but there is no reason why we should not make judicious use of hypotheses. They are extremely useful in directing experimental work, and in clinical work they are a help in controlling observations and in keeping records.

The interest in endocrinological studies all over the world is amazing. It has been estimated that more than 3,000 articles appear on the subject every year. Biedl's work contains a 300-page bibliography! Obviously it is highly desirable that, from time to time, the literature should be summarized. Some men should sift facts,

should combine those that are worthy into groups and should present the results clearly and succinctly to us. Especially valuable for an audience like this, composed of many constituent associations, each representing some specialty, is a symposium of the kind we have had to-day.

Endocrinology should be of interest to every physician and to every surgeon, for the endocrine organs have much to do with the control of phenomena in every part of the body. A rational explanation of these phenomena and of their control is highly desirable, and it is slowly coming. But the domain of endocrinology is, as yet, essentially an empirical domain. The majority of conceptions have come from clinical men who have made empirical observations and reported them. If you think of the contributions made clinically:—Addison's work on the spurarenal glands; the observations of Graves and Basedow on exophthalmic goitre; the studies of Gull on myxedema; Kocher's studies on cachexia thyreopriva, and the work of Marie on acromegaly, you can gauge the importance of clinical empiricism.

Rational explanations are coming from men working in scientific laboratories, but the number of true and certain interpretations is, as yet, amazingly small. These explanations are growing and we welcome them as they are put forth. But I would like to say a word about the unreasonable fear of empiricism, a point that Professor R. G. Hoskins has recently emphasized. Clinicians and laboratory men are at present in danger of too greatly fearing reproach on the ground that their work is empirical. As a result of this fear of reproach, there are often attempts to give rational explanations when it is too early to do so and when the facts do not permit of the union of many diversified phenomena into a single comprehensive formula. That is why we hear referred to as established principles, conceptions that are nothing more than hypothetical constructions. We need, as the first speaker said, more scepticism and less blind confidence, but our scepticism should be an eclectic scepticism.

Clinicians have developed multiple hypothetical constructions as regards the states of the endocrine glands in the attempt to explain clinical syndromes; thus we talk about hyperfunction, about hypofunction, and, again, about dysfunction. Then we consider also the possibilities of combinations of hyper-, hypo-, and dysfunction in the same gland as well as in different parts of the hormone-producing system.

For the validity of the conception of hypofunction we have, for the thyroid gland at least, some very real evidence in the condition sometimes met with after extensive thyroidectomy, namely post-operative myxedema; by substitutive therapy—feeding of desiccated sheep's thyroid—you do away with the symptoms. But when you come to thinking of function as being only moderately rather than markedly decreased, there is great danger clinically of assuming that states exist of which there is difficulty in bringing the proof. We have to be guided by the clinical symptoms observable and by the effects of substitutive therapy. We have had such wonderful examples of the disappearance of symptoms (presumably due to hypofunction of the thyroid and of the pancreas) through the administration of thyroxin and of insulin that we are greatly spurred to the discovery of other hypofunctions that may similarly be compensated for by a well-devised substitutive therapy.

Substitutive therapy is needed only after hypofunction has reached a certain grade. Therefore it is highly desirable that we find methods for determining quantitatively for each gland the degree of hypofunction that exists in any given case. We must, too, learn how to estimate quantitatively the influence of the hormones (or substances containing them) that we use in therapy. Such quantitative studies have been begun; we have listened to a discussion of some examples of them to-day. Clinicians and experimental pathologists now try to measure thyroid hypofunction by determining the degree of retardation of the basal metabolic rate, and they try to measure pancreatic (insular) hypofunction by determining the content of the blood in sugar and by observing the results of insulin therapy. But, as Asher has urged, it should be remembered that the amount of hormonal substance administered and the sphere of its influence measurable are sometimes apparently disproportionate. If the influence increased *pari pasu* with the amount of substance used, the graph of measurable influence would be a straight line, but in cases in which there is only a short interval of hypofunction, the graph would assume the form of a hyperbolic curve. I mention this point in order to show why we must be very careful in interpreting the effects of organotherapy, even when these effects are most carefully observed and recorded.

The clinical conception "hyperfunction" is even less clear than "hypofunction." Take the thyroid gland for example. Who can be sure of precisely what he means when he speaks of "hyperfunc-

tion of the thyroid" or of "hyperthyroidism." Toxic adenoma gives a picture very closely resembling though probably not identical with that of exophthalmic goitre, so that at least two kinds of "hyperthyroidism" have been assumed to exist. The symptoms of the two syndromes differ; the effects of surgical operation are different in the two cases and the effects also of the administration of Lugol's solution are different in the two conditions. How to explain these two supposedly hyperfunctional states of one and the same gland has been found difficult. Some assume that there is hyperfunction in both syndromes but that in exophthalmic goitre there is something additional, perhaps a perversion of function. Others, reasoning from analogy, refer to the glands of external secretion, where hyperacidity of the gastric juice and the excretion of water by the kidney in diabetes insipidus are looked upon as instances of hyperfunction, but of part of an organ rather than of a whole organ; they suggest that the two syndromes of hyperthyroidism may depend upon differences of involvement of partial functions of the thyroid gland.

We come then by an easy transition to the hypothesis of "dysfunction," but that conception, too, is far less clear than we would like it to be. Plummer's ingenious suggestion that in dysfunction we may be dealing with a secretion that is arrested at a stage before it has undergone full chemical evolution and that this partially evolved secretion is poisonous is plausible. Others assume that in the formation of the thyroid secretion several hormones are produced and that there may be a deficiency of some of these even when there is plenty or excess of the others, and so a dys-harmony of thyroid influence results. But not enough facts concerning the physiological action of hormones are available as yet to permit of an adequate critical estimate of the worth of these various conceptions.

A word about uniglandular and pluriglandular syndromes would seem to be desirable. The endocrine glands are undoubtedly closely related to one another functionally and to some extent reciprocally affect one another. Theoretically, every endocrine syndrome must, accordingly, be more or less pluriglandular; but, as yet, we get farther by looking upon the syndromes as predominantly uniglandular and by studying them as such, rather than by laying great stress upon pluriglandular involvement. Only when the symptoms very strongly suggest almost equal disturbance of functions mediated by two or more of the glands, would it seem wise to lay emphasis upon the possible pluriglandular origin of a given syndrome.

One point is very striking in this connection, namely, the great variety of clinical-pathological phenomena that can be made to disappear by the administration of a therapeutic product derived from a single endocrine organ. In myxedema, for example, the dry skin, the dry hair, the retarded chemical changes, the sluggish mentality, the defective intestinal peristalsis can all be influenced by administering one substance, namely, thyroxin. In diabetes mellitus, where there is disturbance of sugar storage, the blood sugar level is high and glycosuria, polyuria, polydypsia, ketosis and disturbance of the metabolism of fatty acids are manifested, all the symptoms and abnormal signs yield to the administration of one substance, insulin. In these instances, the substitutive therapy is uniglandular in principle, and is successful even though scientific study reveals in myxedema and in diabetes mellitus respectively a whole series of disturbed physiological processes!

From a purely theoretical standpoint, the number of endocrinopathic syndromes that might possibly be met with is enormous. Each gland according to current conceptions might be the site of six possible conditions: normal function, hypofunction, hyperfunction, dysfunction, and the combinations of either hypo- or hyperwith dys-function. That is to say, each gland may be the site of one state of normal function and of five states of pathological function. If there are nine glands that yield internal secretions, the possible permutations and combinations mathematically worked out could, according to Professor Hoskins, yield some 10,770,095 different syndromes. Even if one admit the existence of only six endocrine organs, the number of theoretically possible endocrinopathic syndromes would still exceed forty-six thousand. Imagine the joy of the enthusiastic dealer in endocrine products at the thought of providing more than forty-six thousand stock preparations of pluriglandular formulæ! Obviously, it will be wise to exercise caution before becoming over-enthusiastic with regard to pluriglandular therapy.

Fortunately, among all the endocrine products of pluriglandular formula on the market it is the content in thyroid substance alone that is likely to exert any very marked effect; the administration of these multiglandular mixtures that are so much advertised will probably do but little harm as long as the amount of thyroid they contain is not enough to hurt the patient. As soon as the public learns this,

what Dr. Abel has called "the stampede to the pluriglandular gold fields" will, doubtless, subside.

Noteworthy progress is being made just now in the domain of endocrinology. The tartrate of the substance derived from the hypophysis, as prepared by Dr. Abel and his associates, is perhaps the most potent pharmacodynamic substance that is known. It has been found that in dilutions of one part in 18,750 millions it can still cause contraction of the uterus of the guinea pig. Homeopathy has nothing on us! Dr. Cannon's work on the sympathico-suprarenal mechanism in blood-sugar regulation is a valuable contemporary contribution. Dr. Stockard's work on the sex glands, which he described to-day, is dramatic in the results achieved. Dr. Evans and his associates in San Francisco have recently made remarkable observations upon the effects of especially prepared hypophyseal (anterior lobe) extracts; in rats they have been able to produce typical artificial giants. In St. Louis, Allen and Doisy have isolated a hormone from the liquor of the ovarian follicle, which will reproduce the rutting period in animals that have been spayed. Collip, working on the parathyroid glands, has isolated a substance that will control the calcium content of the blood in experimental animals. Kendall, at the Mayo Clinic, is throwing light upon the mode of action of the thyroxin molecule in oxidations. I might mention many other contemporary investigations, but these will suffice to illustrate the significance of the studies of endocrine problems now in progress.

What the future has in store for endocrinology it would be rash to prophesy. The careful study of clinical syndromes by internists will doubtless lead to extensions and revisions in endocrine domains. Biochemists have the task of isolating and determining the nature of all the active principles produced by the endocrine organs. These chemical substances will then have to be synthesized, for the amount of natural substances available will probably not suffice for medical need. Physiologists and pharmacologists will for a long time be supplied with problems for solution in connection with the influences exerted by hormones. In addition to the function of each hormone in normal metabolism the pharmacodynamic effects of each product must also be studied for their own sake, for through such studies pharmaka of surprising therapeutic value are being provided. What physician would now be willing to do without epinephrin in the

treatment of some cases of bronchial asthma, or would consent to be deprived of pituitrin in the therapy of a severe case of diabetes insipidus? Even the obstetrician would scarcely be willing to do without pituitrin, especially since a new method has been devised of obtaining a mild and slow absorption by placing the substance under the tongue, a mode of administration that promises to be more helpful in obstetrical practice than the means used hitherto.

There is good reason to believe that, in the future, endocrine products will be applied in order to control growth and to modify certain constitutional dispositions. In how far such measures will attain to practical value is, as yet, any man's guess. The task before endocrinology is, of course, enormous, and the number of workers in the field far too limited to permit of very rapid progress. I do not think, however, that any one dare say now that more harm than good has come from the study of endocrinology. That, surely, would be a false statement. There is much honest work being done, despite the prevalence of much bombastic speculation. We must, as Dr. Hans Lisser urges, set our faces against ignorant credulity on the one hand and cynical incredulity on the other. Let us all work honestly and harmoniously together in order that knowledge and applications of knowledge in this important field may be steadily advanced.

Discussion by Dr. Harvey Cushing.

DR. HARVEY CUSHING.
Boston, Mass.

It is an Irishism to say that the more one knows about a subject, the less he knows; in other words, the more there is to know. To put it another way, the less he knows, the more he thinks he knows, and the more willing he is to express himself on the subject. I once thought I knew enough about the diseases of the pituitary body to write a book on the subject. I certainly would not venture to do so to-day; and offhand to discuss the ductless glands in general at such a symposium as this is a formidable undertaking.

As our knowledge of the ductless glands has increased, the subject has gained such momentum that like an aeroplane it has finally left the ground altogether to soar on therapeutic wings. But a surgeon of all people has no business to soar—his legs, to use Mr. Lincoln's phrase, must be long enough to reach from his body to the ground and there he must solidly keep his feet (if any of us do who treat patients) for the reason that his particular form of therapeutics is dangerous to life.

We have listened this afternoon to three most stimulating addresses which deal with fundamental principles, and the trifle that I can add concerns but one of the ductless glands and concerns merely the surgery of that particular gland—a very limited field as you can see; and what bi-products of that particular occupation are of general interest, suited to this occasion and audience, will not take me long to point out.

Progress in any subject merely serves to widen the horizon with which one never really catches up. The pituitary gland was negligible in the days when it was supposed merely to be the organ which secreted mucous into the nose. And some few centuries later, when Robert Flood in his *Integrum Morborum* explained the etiology of coryza on the principle of the syphon action between the ventricle and the nose, there were those who scoffed, but they may never have seen a case of cerebrospinal rhinorrhoea. Such were the beginnings of pituitary lore.

How simple was goitre and cretinism when papers on the subject

were read in May of 1897 before the fourth of these triennial congresses! We meanwhile, in the intervening three decades, have advanced far; but could we project ourselves into a meeting of the twenty-third triennial session in 1955, how crude would appear our present conception of thyroid disease! Goitre may by then have passed to the limbo of nigh forgotten diseases, and certainly would long since have passed out of the hands of the surgeon.

But I may say a word in the surgeon's behalf since his rôle in this story when the last chapters come to be written will ever be an important one. Almost the first steps, as you will remember, were surgical ones taken by Kocher and Reverdin—and heroic steps they were. Certain goitres pressed on the trachea causing dyspnoea and slow death by strangulation—a mechanical problem which demanded mechanical relief. It was found possible to give this relief, even found possible with further experience to remove the entire goitre. I need not enumerate the steps which followed: the identification of Kocher's cachexia thyroepriva with myxedema and cretinism; Horsley and Murray's substitution therapy; Halsted's experiments and the consequent recognition of Graves' Disease as a state of hyperthyroidism on which still rests the chief basis of our understanding of this disease; the gradual untangling of the parathyroid mystery; and much else beside.

Now in the case of pituitary disorders, we have arrived at about the Kocher and Reverdin stage, and little further. The tumors, most of them adenomas, press in time on the optic chiasm and threaten loss of vision—again a mechanical process to be relieved by mechanical measures. The surgeon is called in and seeks a way to overcome this calamity. To the person concerned vision is a very important matter and he cares little what is the underlying nature of the disease and what his blood sugar and basal metabolism may show—even that some closely correlated glands have become dystrophic.

This is about where we stand. But meanwhile surgery in the laboratory has shown that deprivation of the gland produces a syndrome of infantilism, adiposity and so on, a condition comparable to myxedema and cretinism which has led us to assume that acromegaly must conversely be due to a state of hyperpituitarism. In these ways we have tended to build up our clinical picture on the basis of what we already know of thyroid disorders. But from a clinical standpoint, the hypophysial problem is by far the more difficult of

the two. The gland is inaccessible and until the sella becomes enlarged or neighborhood symptoms develop, we can hardly be sure (except of course in the presence of acromegaly) that we are actually dealing with a pituitary adenoma. We know very little, indeed, of the histological characteristics of these adenomas, though my associate Dr. Bailey finds that acidophilic granules characterize all the cases of acromegaly in our series; that these granules are never found in the adenomas with hypopituitarism; and that a mixed type of adenoma accompanies those not uncommon clinical syndromes in which traces of overgrowth and hypopituitarism are commingled.

But a study of pituitary disorders is further complicated because the gland consists of two parts, in only one of which have we so far demonstrated, at least up to the time of Herbert Evans' experiments, any experimental evidence of an active substance. Nor do we quite know whether pituitrin can actually be classed as an hormone; nor whether it is formed in the pars nervosa; nor whether it actually escapes into the cerebrospinal spaces.

Just now there is a discussion on the boards as to whether certain symptoms such as the polyuria, adiposity, and somnolence which accompany certain pituitary tumors may not actually be neurogenic in origin and be due to some lesion of the cells of the adjacent hypothalamus. This may well enough be so; but I think only in the sense that exophthalmic goitre may be neurogenic, even diabetes mellitus, as some suggest in view of the inconstant and trifling changes demonstrable in the islets of fatal cases of that disease. We have a long way to go. Except for the use of pituitrin in diabetes insipidus, we have as yet no satisfactory replacement therapy for pituitary insufficiency exhibited in its most striking form in the skeletal and sexual infantilism in childhood.

Evans' experiments, to be sure, are encouraging, but no known glandular extracts have as yet been shown to be capable of stimulating growth in clinical cases. This we have learned to our great disappointment after subjecting a pituitary dwarf for a long period to intraperitoneal injections of anterior lobe extract. When Professor Abel has finally succeeded in elaborating the active principle of the pars nervosa, I sincerely hope he will turn his attention to the pars distalis. It is an important structure. We have learned enough about its extractives to know that there may possibly be two substances—one which has a prompt effect on checking the oestral cycle, and the other, a more elusive substance which may be the hormone

of growth. With potent substances like Abel's epinephrin, Kendall's thyroxin, Banting's insulin, and the promised parathyroxin of Hanson and Collip, we can be encouraged to believe that active principles from other glands may be found; and I have always felt that in the anterior lobe of the hypophysis may be found the key which will explain their interrelations.

But this begins to sound visionary—as though I too were getting off the ground instead of minding the surgeon's principal business, in matters hypophysial, of seeing that the victims of pituitary adenomas so far as possible preserve their sight through operative measures.

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